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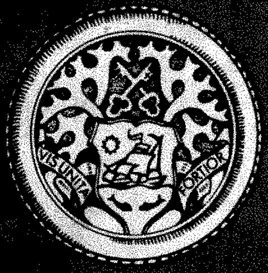

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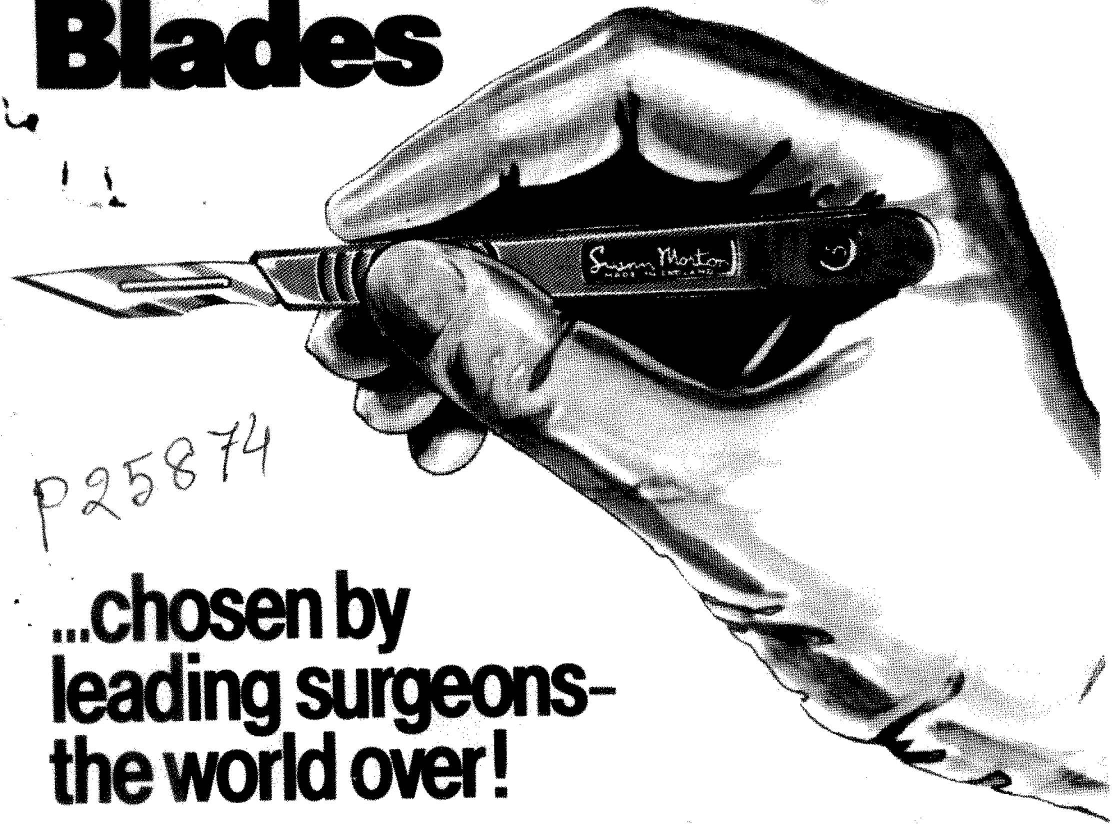

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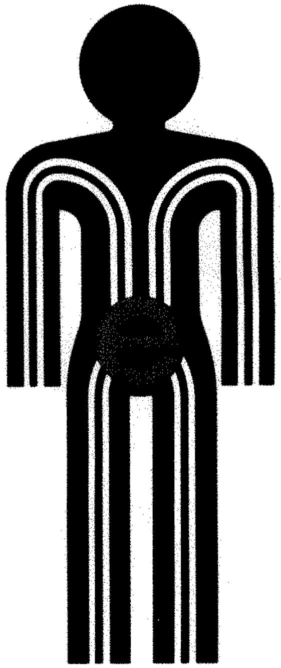

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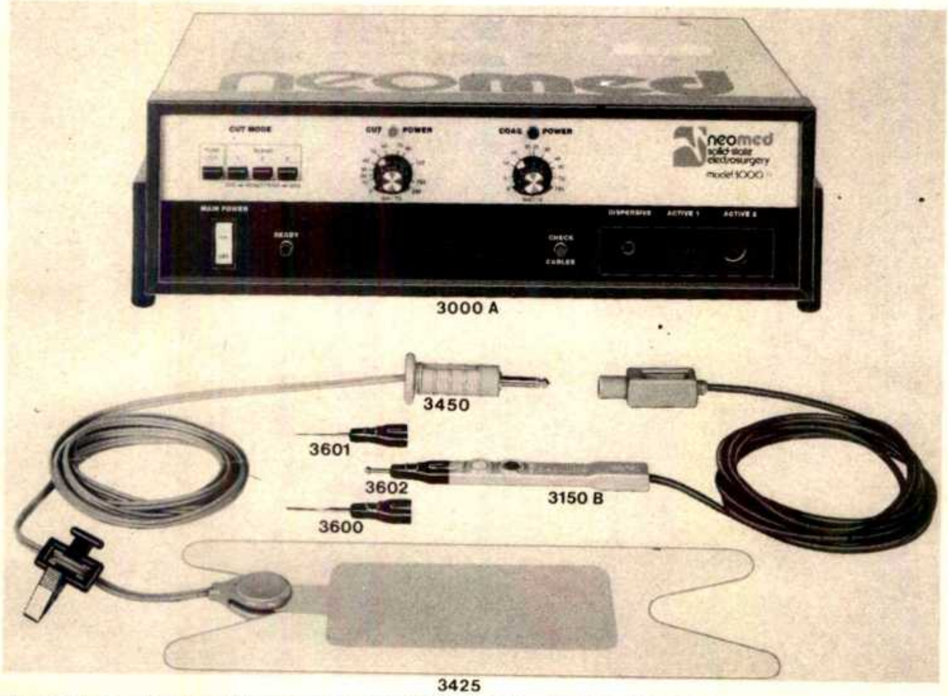

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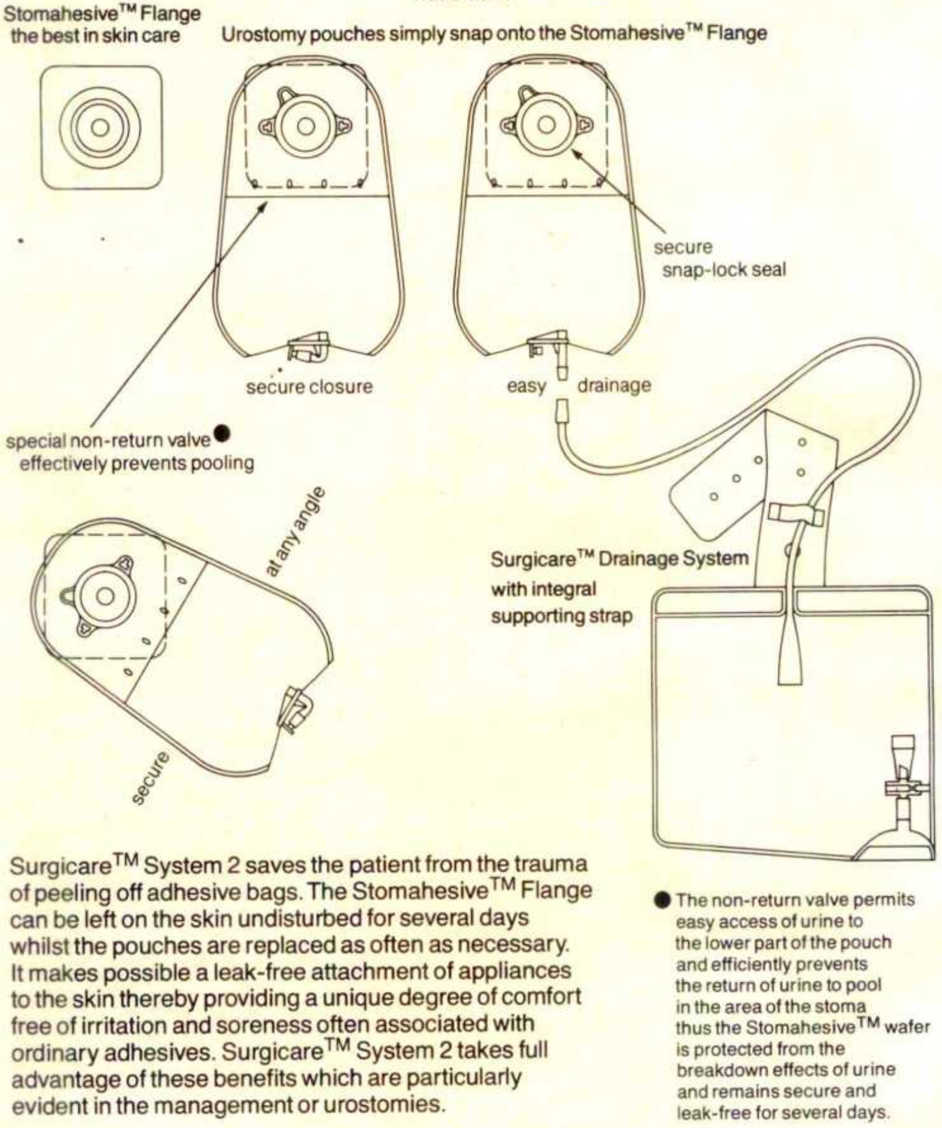
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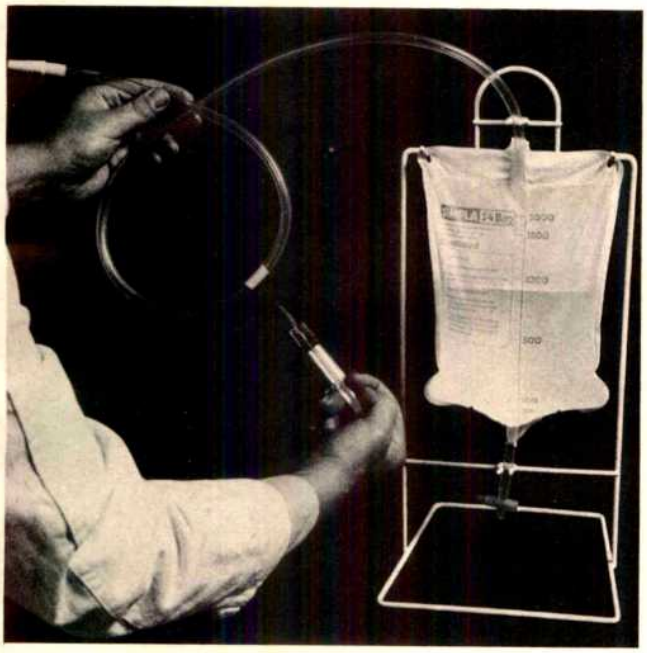

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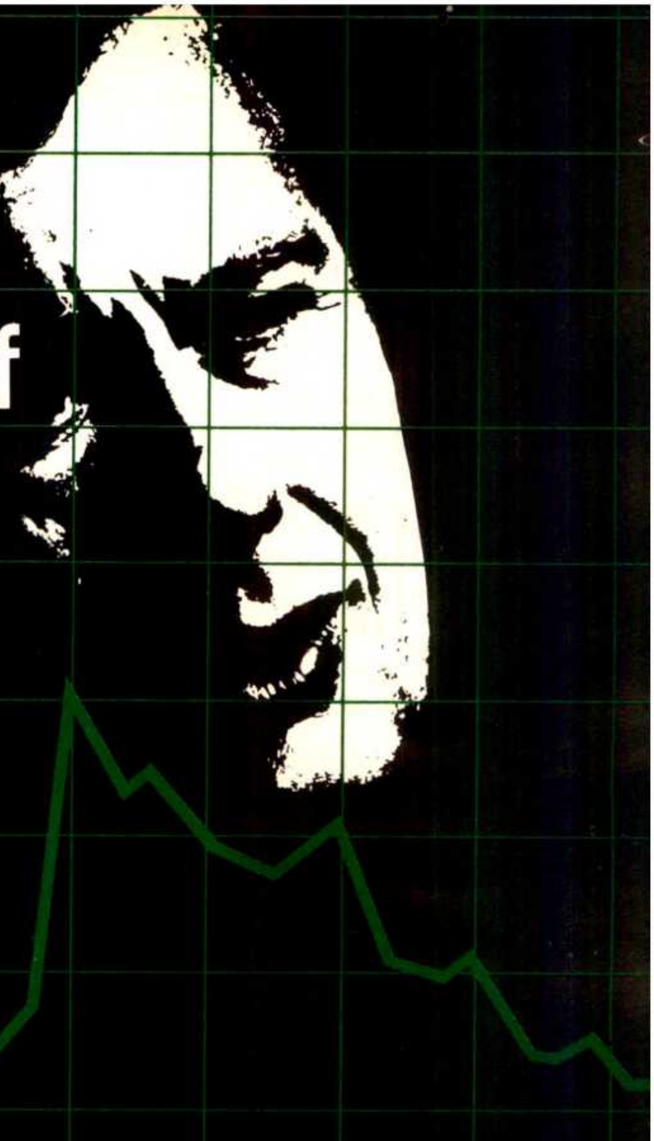

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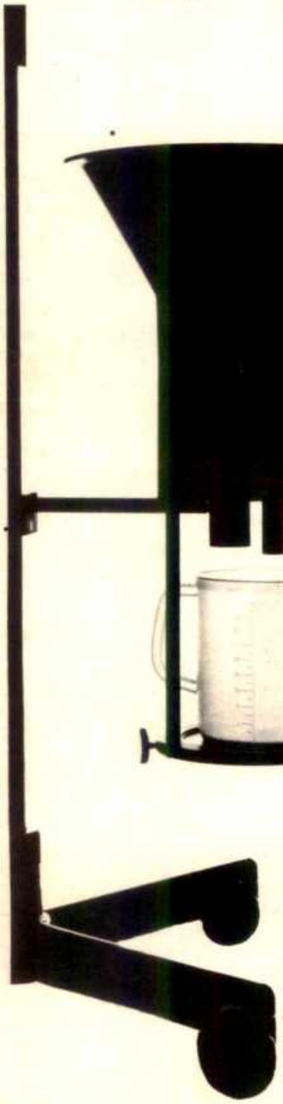

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Megacalices—How Broad a Spectrum?

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Summary—Ten patients with a suspected diagnosis of megacalices have had pressure-flow studies to confirm or exclude obstruction. Eight had no evidence of obstruction and amongst these there were 2 patients with a non-obstructed megaureter. Two patients showed evidence of obstruction and remain a dilemma from a management viewpoint. If "megacalices" is used simply as a descriptive term, then the spectrum of disease is wider than previously suspected.

The condition of megacalices has been described as an underdevelopment of the renal pyramids in association with oversized calices (Talner and Gittes, 1972). It may affect one or both kidneys. One of the prime requisites for the diagnosis has been the absence of obstruction. This was stressed in the early description of this condition by Puigvert (1963) and in subsequent discussions (Talner and Gittes, 1972, 1974).

In the early studies the exclusion of obstruction was by urography, ureterography and standard isotope renography. Although in some cases the renograms suggested some delayed emptying, it was assumed to be due to gradual mixing of the isotope within the larger volume of the kidney and not due to obstruction.

During the last 5 years the need to diagnose even minor degrees of obstruction accurately has been emphasised. Doubt has been cast on the ability of the above methods to do this and newer methods have been developed such as sophisticated radioisotope studies measuring parenchymal transit times, or by using diuresis renography and by direct measurement of the dynamics within the kidney by means of percutaneous pressure-flow studies. Each method has its own advantages and we have concentrated on direct dynamic assessment. Although such studies are invasive, they are generally accepted as giving an accurate appraisal of the degree of obstruction. In the light of these developments we have studied a few patients with suspected megacalices to determine the absence or presence of obstruction and to see to what extent this group of patients is homogeneous.

Patients

We studied only those patients who had kidneys with the urographic appearance of megacalices. In 8 of the 10 patients the ureter was entirely normal, but in 2 the ureter was wide with what proved, on pressure-flow studies, to be a primary non-obstructed megaureter. We have included these 2 patients in this series because previous authors have commented upon the association of megacalices and non-obstructed wide ureters (Von Niederhausern and Tuchschmid, 1971; Talner and Gittes, 1974). We have excluded all patients in whom there was a strong suspicion of a pelvi-ureteric junction obstruction.

The essential urographic features in all 10 cases were "dilated" calices, but with no infundibular narrowing and a symmetrical loss of renal parenchyma suggestive of medullary loss (Figs. 1 and 2). There was no obvious site of obstruction within the upper urinary system as judged by the ready filling of the ureter and transit to the bladder. Four of the 10 patients had renography with hydration and all 10 underwent percutaneous pressure-flow studies (Whitaker, 1973, 1979).

Results

The pressure-flow studies showed that with perfusion at 10 ml per min, 8 of the kidneys showed normal pressures as defined by a pressure drop from kidney to bladder of 15 cm of water or less. Figures 1 and 2 illustrate 2 patients with typical megacalices. In the 2 patients in this group who had renograms the study confirmed the absence of obstruction. Two patients had raised pressures indicative of obstruction.

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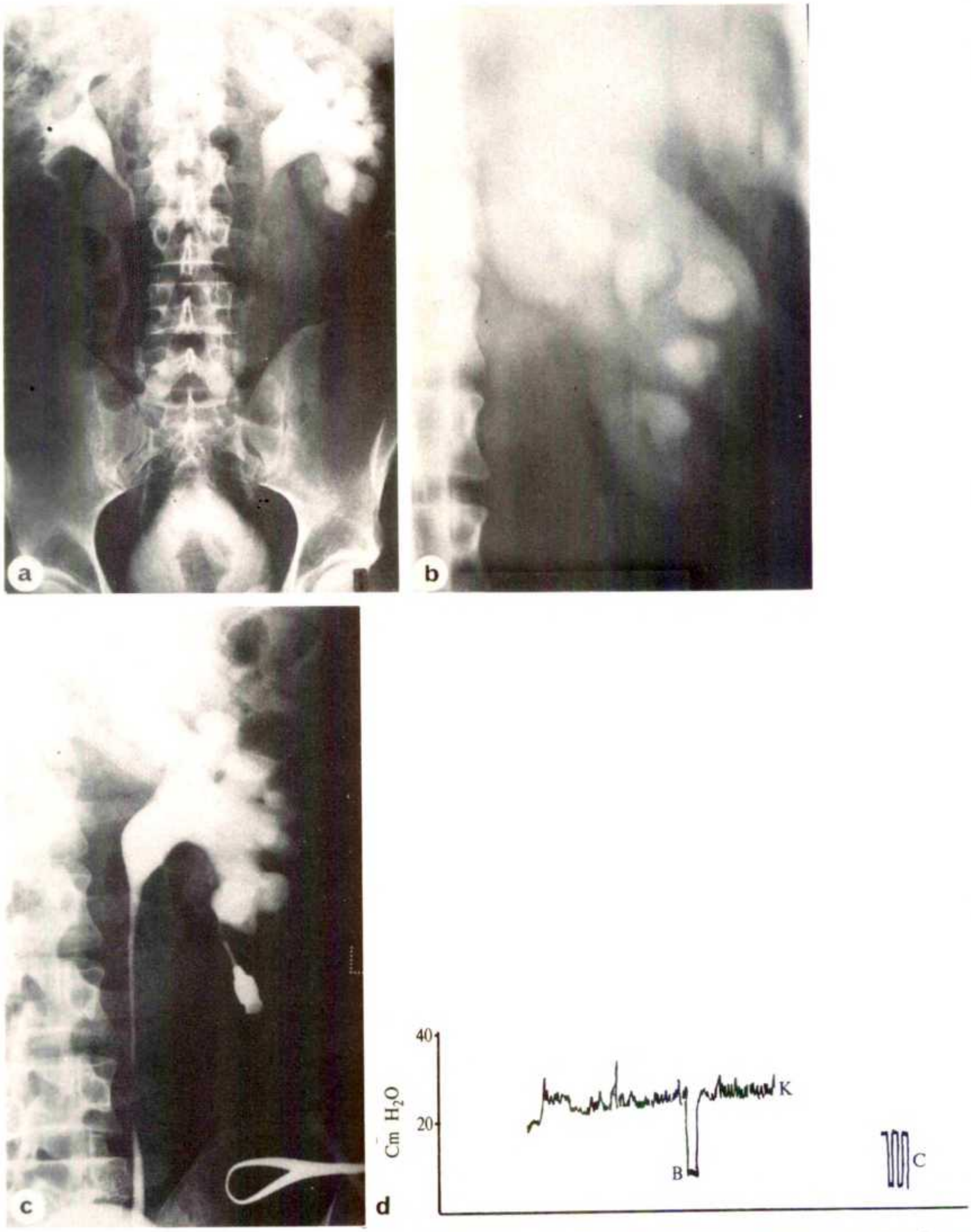

Fig. 1 A 33-year-old male (K.K.) found to have transient mild hypertension on a routine medical examination. No urinary symptoms. (a) IVU—left megacalices, normal ureteric filling. (b) Early tomogram showing medullary loss. (c) Antegrade pyelogram. (d) Pressure tracing showing a relative pressure of 4 cm water at 10 ml per min.

K = Pressure in kidney.
B = Pressure in bladder.
C = Resistance of cannula.

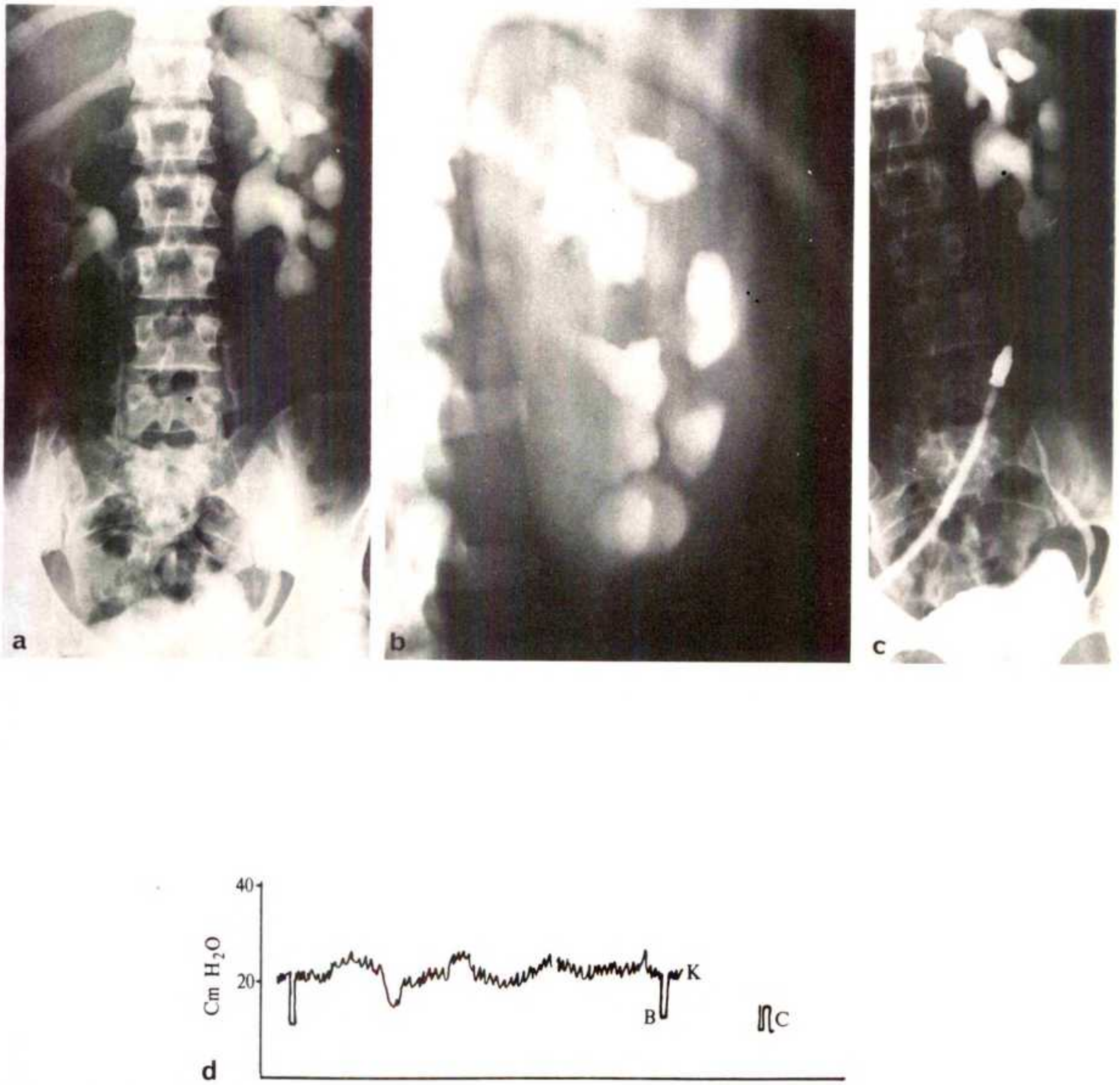

Fig. 2 A 30-year-old female (S.M.) with a questionable urinary tract infection during pregnancy. (a) IVU—left megacalices, normal ureteric filling. (b) Early tomogram showing medullary loss. (c) Antegrade pyelogram. (d) Pressure tracing showing a relative pressure of 5 cm water at 10 ml per min.

K = Pressure in kidney.
B = Pressure in bladder.
C = Resistance of cannula.

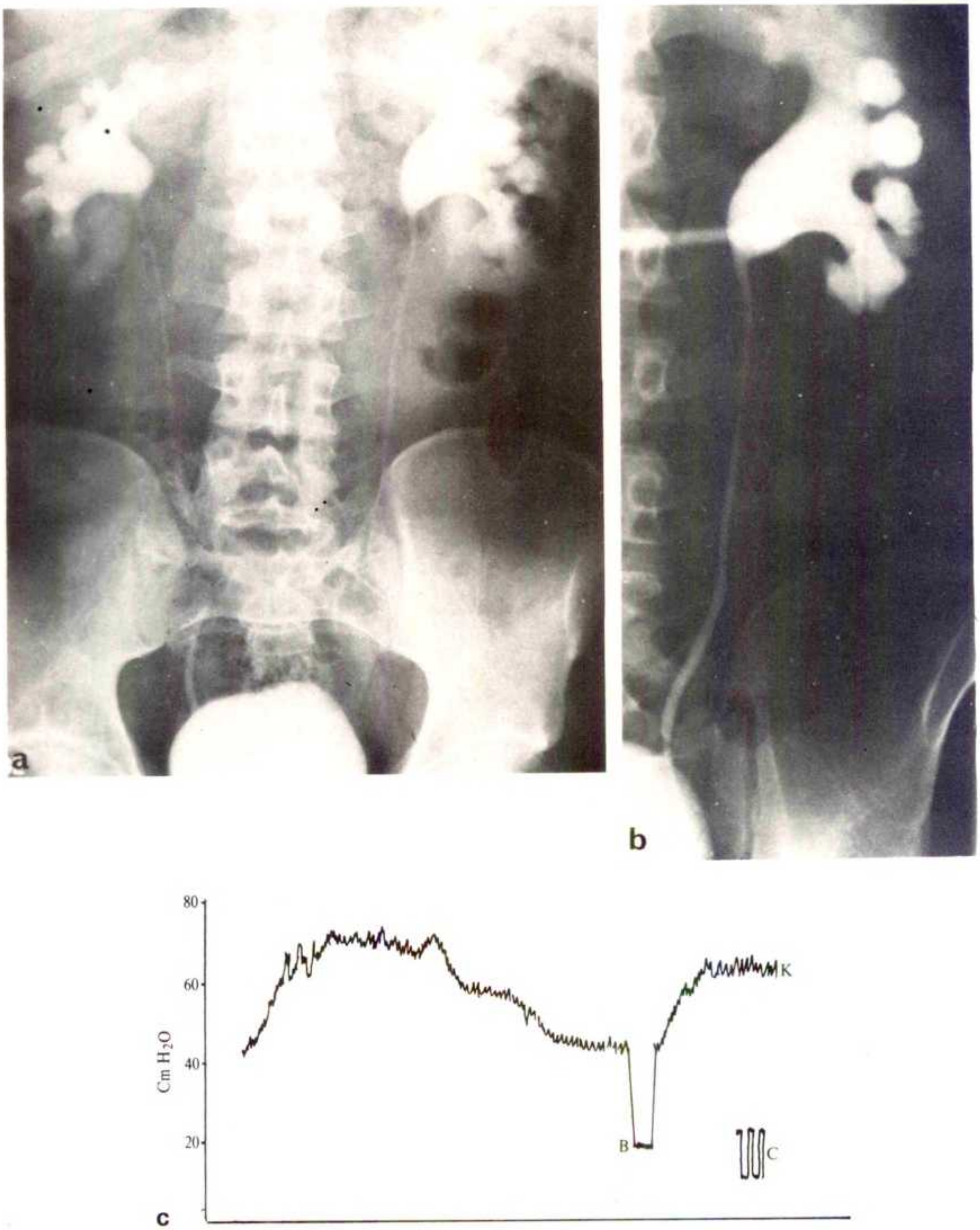

Fig. 3 A 28-year-old obese patient (S.S.). (a) IVU suggestive of bilateral megacalices but with narrow ureters. (b) Antegrade pyelogram: ureters show good peristalsis but remain thin. (c) Pressure tracing showing a relative pressure of 36 cm water at 10 ml per min.

K = Pressure in kidney.
B = Pressure in bladder.
C = Resistance of cannula.

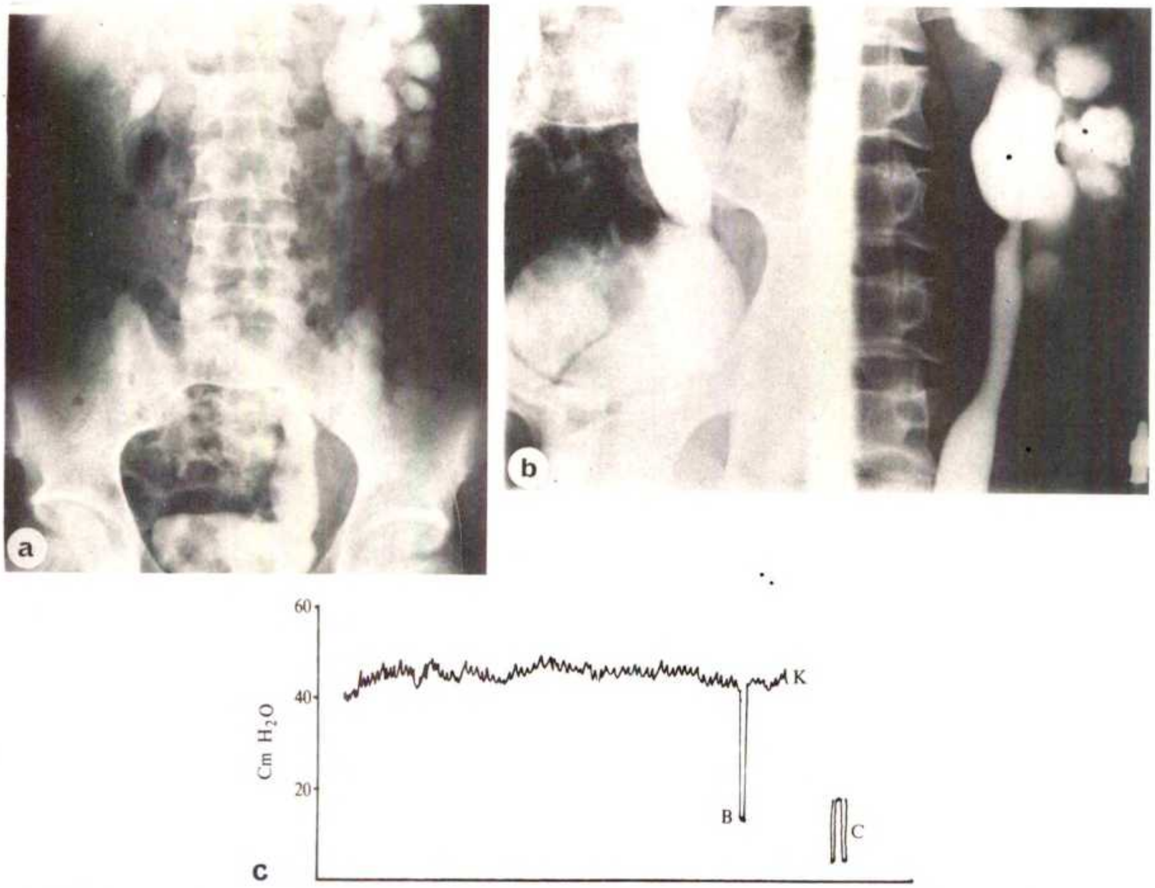

Fig. 4 A 15-year-old boy (P.L.) who had mild haematuria following a blow to the left side. (a) IVU suggestive of megacalices but with a wide ureter. (b) Antegrade pyelogram. The ureter empties readily into the bladder. (c) Pressure tracing showing a relative pressure of 15 cm water at 10 ml per min.

K = Pressure in kidney.
B = Pressure in bladder.
C = Resistance of cannula.

The first obstructed kidney remains a diagnostic problem in that the relative pressure was 26 cm of water, but there was no obvious site of obstruction to which we could direct surgical relief. His urographic appearances have not changed over 7 years. A hydrated renogram did not confirm our dynamic findings of obstruction.

The second patient showing obstruction was the more curious and perplexing of these 2 (Fig. 3). He was an overweight 28-year-old who was first seen at the age of 18 years with what was probably an attack of right renal colic. An intravenous urogram at that time showed "bilateral hydronephrosis". Since then he has had several further urograms showing no appreciable change. Over the last 9 years he has had 2 further episodes of mild right-sided pain and one episode of transient haematuria. A hydrated renogram in 1977 suggested good overall function, but with prolonged transit times suggesting a mild degree of obstruction on both sides. An antegrade pyelogram was performed on the right side and this showed a pressure differential between the kidney and bladder of 36 cm of water at 10 ml per min, indicative of obstruction. Both ureters were very narrow, but exhibited normal motility and did not resemble retroperitoneal fibrosis. Several experienced radiologists have independently stated that the urographic appearances are very suggestive of megacalices. It is evident that this patient has a degree of obstruction but the exact site is not apparent and it seems likely that the narrow ureters represent an overall increased resistance.

One of the 2 patients with a wide ureter is illustrated in Figure 4. He exhibits the urographic appearances of megacalices in association with a non-obstructed megaureter.

Discussion

Megacalices have been defined as a discrete entity with a typical pyelographic appearance and no evidence of obstruction. If this strict definition is adhered to, only 6 of our patients would meet the requirements for this diagnosis. The 2 patients with wide ureters could be described as non-obstructed megaureters with accompanying pelvi-caliceal changes. In the remaining 2 patients the urographic appearances are typical of megacalices, but in both there was evidence of obstruction. In one of these patients there remains some doubt as to the significance of the obstruction in view of the renographic evidence. In the other patient with bilateral thin ureters, there is unequivocal evidence of obstruction confirmed by both renography and dynamic studies. However, the exact level of the obstruction and whether operative relief is necessary remain uncertain.

If, however, megacalices is simply used as a descriptive term, then all 10 of these patients can be included whether or not they exhibit obstruction. This would suggest that perhaps there is a wider spectrum of this condition than previously suspected and maybe we should be forced to accept that lesser degrees of obstruction are compatible with the diagnosis of megacalices. If, indeed, the aetiology of this condition is a "burnt out obstruction", as has been suggested, then it is perhaps not surprising that some cases may still show some evidence of this obstruction (Johnston, 1973). This theory, although convenient, is probably too simplistic.

Acknowledgement

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Urolithiasis in the Sudan. Studies on a Stone-prone and a Stone-free Population

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Summary—Biochemical studies were performed on 80 adult males with renal stones and 24 controls from Northern Sudan. Similar studies were performed on 44 controls from Southern Sudan, where urinary stones rarely occur.

No significant differences between stone formers and controls from Northern Sudan were found regarding serum uric acid, phosphate, alkaline phosphatase, total protein, albumen, daily urine calcium or uric acid. Similarly, no significant difference was found between the 2 groups in the incidence of hypercalciuria, hyperuricaemia or hyperuricosuria. The serum calcium was significantly higher in stone formers.

The mean serum and daily urine calcium were significantly lower, and the mean serum and daily urine uric acid were significantly higher in controls from Southern Sudan compared to either stone formers or controls from Northern Sudan. The mean daily urine volume was significantly higher in Southern controls compared to Northern controls.

The increased prevalence of stone formers in Northern Sudan appears to result from the higher calcium output in the urine and the lower urine volume in the North compared with the South.

Urinary stones are generally considered to be uncommon amongst Africans (Blacklock, 1976). This is usually attributed to dietary rather than genetic causes (Modlin, 1967).

Both renal and vesical stones are common in Northern Sudan. This part of the country is hot and dry throughout most of the year. Almost half of this region is part of the hot, arid African Sahara and the population is of Afro-Arab stock.

Stones are rare in Southern Sudan, which is inhabited by pure Africans. This region is cool and fairly humid throughout the year.

This paper presents the results of biochemical studies in consecutive adult males with upper urinary tract stones from Northern Sudan. The results are compared to those found in controls from the same region and controls from Southern Sudan.

Patients and Methods

Eighty consecutive adult males with renal or ureteric stones were investigated at the Department of Urology, Khartoum North Hospital, Sudan. The diagnosis of stone was made radiologically or by recovery of the stone after an attack of renal colic. The patients came from different parts of Northern Sudan and all social classes were represented. The mean age was 39 years. Twenty-five patients had more than one stone on the same side and 6 had bilateral stones. In 12 patients the stones were recurrent. Seventeen stones were of the staghorn variety. Only 6 patients had anatomical abnormalities of the urinary tract, including some due to bilharziasis.

Twenty-four male controls from Northern Sudan and 44 male controls from the town of Juba and the adjacent village of Bilinyang in Southern Sudan were similarly investigated. The mean age for the 2 control groups was 39 and 38 years respectively. None of the controls had past or present evidence of stones.

Only patients or subjects with normal renal function, as judged by blood urea, were included in the study.

Venous blood was taken, without a tourniquet, after overnight fasting. Two 24-h collections of urine were taken from each patient while on a normal diet, one in toluene and the other in N/10 hydrochloric acid for the assessment of uric acid

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and calcium respectively. The adequacy of the 24-h urine collection was tested by measuring urine creatinine. Those found to have less than 1.5 g creatinine were repeated or excluded.

The serum inorganic phosphate, total proteins, alkaline phosphatase and uric acid in both serum and urine were measured using standard methods (Wootton, 1974). Serum albumen was measured by the dye-binding method using bromocresol green. Serum and urine calcium were measured by Perkin-Elmer atomic absorption spectrophotometry (Model 360). In all samples showing hyperuricaemia or hyperuricosuria, the measurements were confirmed by the Uricase method (Wootton, 1974). Serum calcium was corrected for serum albumen level.

Results

All patients with hypercalcaemia (more than 2.75 mmol/l) and those with anatomical abnormalities of the urinary tract were excluded. Table 1 shows the results in the remaining patients and comparison with the 2 control groups.

Serum Calcium

The mean serum calcium for patients (2.43 mmol/l; 9.7 mg/100 ml) was significantly higher ($P < 0.02$) than that for Northern controls (2.28 mmol/l; 9.1 mg/100 ml). The mean for both groups was within the normal range (2.13-2.75 mmol/l; 8.5-11 mg/100 ml).

The mean serum calcium for the Southern controls (2.05 mmol/l; 8.2 mg/100 ml) was in the hypocalcaemic range and was significantly lower than that for either group from Northern Sudan ($P < 0.001$ in each case).

24-h Urine Calcium

Although the mean 24-h urine calcium in patients (3.35 mmol; 134 mg) was higher than that of Northern controls (3.13 mmol; 125 mg), the difference was not statistically significant ($P > 0.5$).

Six patients (9.5%) and none of the Northern controls excreted more than 7.5 mmol (300 mg) of calcium per day and were therefore hypercalciuric according to European standards (Hodgkinson and Pyrah, 1958).

Table 1 Comparison Between Adult Males with Renal Stones and Controls from Northern and Southern Sudan

		No.	*Mean and SD*	*t value*	*P*
Serum calcium	P	66	2.43 ± 0.18 mmol/l (9.7 ± 0.7 mg/100)	P/NC 2.4939	<0.02
	NC	21	2.28±0.33 mmol/l (9.1±1.3 mg/100)	NC/SC 3.8011	<0.001
	SC	44	2.05 ± 0.18 mmol/l (8.2 ± 0.7 mg/100 ml)	P/SC 10.7999	<0.001
Serum phosphate	P	57	1.21 ± 0.26 mmol/l (3.8 ± 0.9 mg/100)	P/NC 1.716	>0.05
	NC	20	1.09 ± 0.18 mmol/l (3.4 ± 0.6 mg/100)	NC/SC 0.097	>0.1
	SC	43	1.1 ± 0.2 mmol/l (3.5 ± 0.5 mg/100)	P/SC 1.995	>0.05
Serum alkaline phosphatase	P	51	60.8 ± 22.4 iu/l (8.1 ± 3.0 KA units/100 ml)	P/NC 1.057	>0.1
	NC	21	66.8 ± 20.3 iu/l (8.9 ± 2.7 KA units/100 ml)	NC/SC 1.004	>0.1
	SC	43	60 ± 32 iu/l (8.0 ± 4.3 KA units/100 ml)	P/SC 0.273	>0.5
Serum albumen	P	51	35.3 ± 6.2 g/l	P/NC 0.455	>0.5
	NC	22	34.9 ± 4.4 g/l	NC/SC 0.915	>0.1
	SC	44	33.3 ± 7.7 g/l	P/SC 1.576	>0.1
Serum uric acid	P	69	0.33 ± 0.08 mmol/l (5.5 ± 1.4 mg/100)	P/NC 0.113	>0.5
	NC	21	0.34 ± 0.09 mmol/l (5.6 ± 1.5 mg/100)	NC/SC 3.666	<0.001
	SC	44	0.43 ± 0.10 mmol/l (7.1 ± 1.6 mg/100)	P/SC 5.633	<0.001
24-h urine calcium	P	63	3.35±2.40 mmol (134±96 mg)	P/NC 0.444	>0.5
	NC	24	3.13 ± 1.28 mmol (125 ± 51 mg)	NC/SC 3.023	<0.01
	SC	44	2.03 ± 1.43 mmol (81 ± 57 mg)	P/SC 3.238	<0.01
24-h urine uric acid	P	67	1.78 ± 1.03 mmol (296 ± 171 mg)	P/NC 0.606	>0.5
	NC	23	1.63 ± 0.80 mmol (271 ± 133 mg)	NC/SC 4.971	<0.001
	SC	42	5.79 ± 3.94 mmol (965 ± 657 mg)	P/SC 8.092	<0.001

P = Patients with stones.
NC = Controls from Northern Sudan.
SC = Controls from Southern Sudan.

Table 2 shows the number of patients and Northern controls with hypercalciuria at arbitrary upper normal limits of daily calcium excretion. It shows that at all of the values there was no significant difference in the incidence of hypercalciuria between stone formers and Northern controls.

The mean 24-h urine calcium for Southern controls (2.03 mmol; 81 mg) was significantly lower than that for either patients or controls from Northern Sudan ($P < 0.01$ in each case). Thirteen subjects (30%) in this group excreted less than 1.25 mmol (50 mg), 33 (75%) excreted less than 2.5 mmol (100 mg) and 42 (95%) excreted less than 3.75 mmol (150 mg) of calcium per 24 h.

Figure 1 shows a comparison between the serum and urine calcium of the 3 groups.

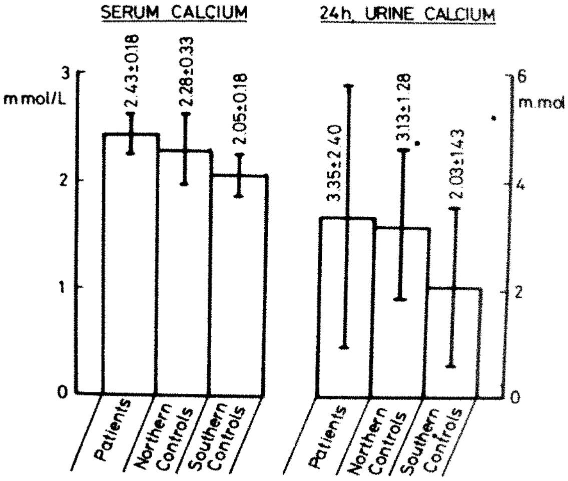

Fig. 1 Serum and 24 h calcium in the 3 groups.

Serum Phosphate, Alkaline Phosphatase, Total Protein and Albumen

No significant difference was found between the 3 groups regarding the means of these parameters.

Serum Uric Acid

There was no significant difference between the mean serum uric acid of patients (0.33 mmol/l; 5.5 mg/100 ml) and that of Northern controls (0.34 mmol/l; 5.6 mg/100 ml) ($P > 0.5$). Three patients (4%) and one control (4%) had hyperuricaemia (>0.45 mmol/l; 7.5 mg/100 ml). No significant difference existed between patients and Northern controls regarding the number with hyperuricaemia ($\chi^2 = 0.006$; $P > 0.5$).

The mean serum uric acid for Southern controls (0.43 mmol/l; 7.1 mg/100 ml) was significantly higher than that for either group from Northern Sudan ($P < 0.001$ in each case). Fourteen subjects (32%) in this group had serum uric acid levels greater than 0.45 mmol/l (7.5 mg/100 ml).

The upper limit of normal serum uric acid (0.45 mmol/l) was derived from unpublished work by some of us (E.M.A.W. and A.H.H.) on a population from Northern Sudan.

Table 2 Hypercalciuria in Patients and Controls from Northern Sudan

24-h urine calcium	*Patients*	*Controls*	χ^2	*P*
>7.5 mmol (300 mg)	6 (9.5%)	0	2.4550	>0.1
>5.7 mmol (227 mg)	9 (14%)	1 (4%)	1.7493	>0.1
>5.0 mmol (200 mg)	12 (19%)	2 (8%)	1.4776	>0.1
>3.75 mmol (150 mg)	17 (27%)	7 (28%)	0.0414	>0.5

5.7 mmol represents the mean 24-h urine calcium of controls. + 2 SD.

24-h Urine Uric Acid

There was no significant difference between the mean 24-h urine uric acid of patients (1.78 mmol; 296 mg) and that of controls (1.63 mmol; 271 mg) ($P > 0.5$). Two patients (3%) and none of the Northern controls excreted more than 4.5 mmol (750 mg) of uric acid per 24 h. There was no significant difference between patients and Northern controls regarding the number with hyperuricosuria ($\chi^2 = 0.7022$; $P > 0.01$).

The mean 24-h urine uric acid for the Southern controls (5.79 mmol; 965 mg) was significantly higher than that for either patients or Northern controls ($P < 0.001$ in each case). Twenty-one subjects (50%) in this group excreted more than 4.5 mmol (750 mg) of uric acid per 24 h.

Figure 2 compares the serum and urine uric acid of the 3 groups.

24-h Urine Volume

The mean 24-h urine volume for the Southern controls (1328 ± 504 ml) was significantly higher than that of Northern controls (899 ± 531 ml) ($P < 0.01$). The mean 24-h urine volume for stone formers was 1870 ± 1832 ml. This was significantly higher than that for Northern controls ($P < 0.02$) but not significantly higher than that for Southern controls ($P > 0.05$).

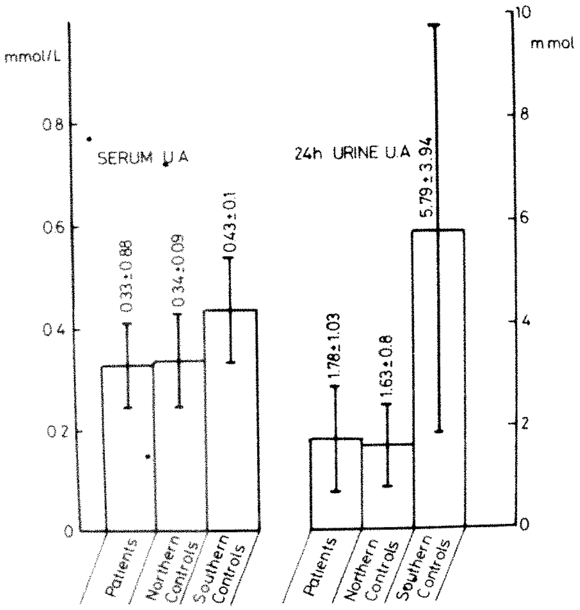

Fig. 2 Serum and 24 h urine uric acid in the 3 groups.

Discussion

Quantitative analysis has previously shown that 75% of adult renal stones in Sudanese were calcium oxalate and 12.5% were calcium oxalate + calcium phosphate (Kambal *et al.*, 1979a and b). These patients can therefore be considered as idiopathic calcium stone formers.

This study shows that there was no difference between patients with renal stones and controls from Northern Sudan with regard to all parameters except serum calcium.

The higher mean serum calcium of the stone formers is not related to the aetiology of their stones, since it was not associated with a correspondingly higher urine calcium. Studies from other developing countries indicated no significant difference between the mean serum calcium of patients with stones and that of normal controls (Shahjehan and Raman, 1971; Raman and Sreenevasan, 1972).

Our findings on daily calcium excretion agree with those of some workers (Papadimitriou *et al.*, 1968; Welshman and McGeown, 1975) but disagree with several others who reported a significantly higher daily calcium excretion in stone formers (Evans *et al.*, 1967; Raman and Sreenevasan, 1972; Robertson and Morgan, 1972).

Idiopathic hypercalciuria has been reported in 31% (Williams and Chisholm, 1976) to 42% (Yendt, 1970) of patients with calcium stones. Our results show that only 9.5% of our stone formers excreted more than 7.5 mmol (300 mg) of calcium per day. The upper limit of daily calcium excretion by normal individuals in the Sudan is probably lower than 7.5 mmol because of the lower calcium intake by Sudanese compared to Europeans. Nonetheless, no significant difference in the incidence of hypercalciuria was shown between stone formers and controls at arbitrary upper limits of normal down to 3.75 mmol per day.

It has been shown that at low calcium intake there was little difference in urinary calcium excretion between stone formers and controls (Peacock *et al.*, 1967). The same authors found that hypercalciuria was detectable only at a moderately high calcium intake. The low calcium intake by Sudanese may therefore explain the low incidence of hypercalciuria amongst our stone formers.

The mean daily calcium excretion by subjects from Southern Sudan was almost identical to that of the South Africa Bantu (Modlin, 1967). The inhabitants of this part of Southern Sudan are cultivators. They have few cattle or sheep and their consumption of milk and other dairy products is minimal. In addition, the scarcity of sunshine may reduce vitamin D synthesis. This may explain their hypocalcaemic mean serum calcium and their very low daily calcium excretion.

The daily urine volume in dwellers of Northern Sudan is subject to wide seasonal variation. Previous studies indicated that, in adults, the daily urine volume may vary from 594 ml in the hot season to 1515 ml in the colder season (Kambal, 1978). Such a wide variation probably does not occur in Southern Sudan, where the mean monthly temperature does not vary by more than 4°C throughout the year. The mean urine volume in Northern controls was significantly lower than that in Southern controls. Urine was collected from Northern controls throughout the year; their mean urine volume would have been even lower had the collection been confined to the hot season.

The large urine volume in stone formers is due to the fact that they tend to drink large amounts of water once they have been told that they have stones.

An adequate calcium concentration in urine is essential for calcium salt precipitation (Nordin, 1973). The very low urine calcium and the relatively high urine volume shown by subjects from Southern Sudan must therefore be important factors in their immunity to calcium stone disease. The relatively high urine volume in these subjects is due partly to the cooler and more humid climate and partly to their consumption of large amounts of locally made alcoholic beverages as part of their diet.

The low daily urine volume passed by Northern Sudanese because of the hot dry climate is probably an important factor in their susceptibility to urinary stones. Although the daily calcium output is lower than that of Europeans, the low urine volume may result in a calcium concentration higher than that found in Europeans. Under similar climatic conditions, Tinckler (1966) described a state of voluntary dehydration with oliguria when subjects failed to drink enough water to meet their requirements. In Israel, oliguria and dehydration in subjects living in hot arid zones have been found to be associated with an increased prevalence of urolithiasis (Frank *et al.*, 1963). Our observations have shown that the prevalence of urolithiasis in different parts of the Sudan is inversely related to the relative humidity (Kambal *et al.*, 1979a).

Our results indicate that while hyperuricaemia or hyperuricosuria may occur in a small percentage of patients with calcium stones, there was no significant difference in this respect between stone formers and controls. Whilst our findings are in agreement with those of Hodgkinson (1976), they do not support earlier reports that uric acid abnormalities were very frequent amongst calcium stone formers (Smith *et al.*, 1969; Dent and Sutor, 1971; Coe and Kavalack, 1974).

It has been suggested that uric acid abnormalities may play a role in the aetiology of calcium stone disease (Coe and Raisen, 1973). Ibrahim (1975) reported hyperuricaemia (>6 mg/100 ml, 0.36 mmol/h) in 20% of adult Sudanese males in Khartoum and implied that this may have a bearing on the aetiology of urinary stone formation in the Sudan. Our findings show a much lower incidence of hyperuricaemia in both stone formers and controls and indicate that uric acid abnormalities play no important role in the aetiology of adult renal stones in the Sudan.

Hyperuricosuria has been reported to be the cause of stones in some patients with leukaemia and lymphoma (Krakoff and Meyer, 1965) and in some gouty subjects (Gutman and Yu, 1968). The findings in controls from Southern Sudan, who represent a stone-free population, indicate that hyperuricosuria alone does not lead to stone formation. Gutman and Yu (1968) stated that hyperuricosuria plays an important part in uric acid nephrolithiasis only when it is not accompanied by a proportionate expansion in the urine volume. The mean urine volume in subjects from Southern Sudan was less than the 1500 ml generally accepted as being the normal daily urine volume in temperate climates. Our data are not yet completed regarding the urine pH and crystalluria in these subjects. Unless their urine pH is sufficiently high, an inhibitor of uric acid crystallisation or crystal growth may be involved.

In conclusion, although stone formers showed no significant hypercalciuria, the latter might have been masked by the low calcium intake. Dehydration with low urine volume, when the urine calcium concentration may reach high levels despite the low daily calcium excretion, is another probable lithogenic factor in Northern Sudanese. In Southern Sudan the extremely low calcium excretion and the relatively high urine volume seem to militate against the development of stones.

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Papillary Adenocarcinomatous Degeneration Occurring in a Multilocular Renal Cyst

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Summary—A multilocular cyst of the kidney in an adult with malignant papillary adenocarcinomatous transformation is described. The histogenesis and prognosis of multilocular cysts are discussed with special reference to their relationship with Wilms' tumour.

Multilocular cyst of the kidney is not common. Only 76 cases have been published to date (Baldauf and Schulz, 1976; Datnow and Daniel, 1976; Jeffords *et al.*, 1976), some associated with Wilms' tumours (Uson *et al.*, 1960; Chang, 1976) and some with Grawitz's tumours (Kawamura and Miyakawa, 1969; Posso *et al.*, 1973).

The macroscopic and microscopic diagnostic criteria suggested by Powell *et al.* (1951) emphasise their unilateral, solitary and multilocular character. The cysts should not communicate with the pelvis and the locules should not communicate with each other. The cysts should be lined by epithelium, no other elements of the renal parenchyma should be present inside the cyst, and any remaining kidney parenchyma should be normal.

These criteria were modified by Boggs and Kimmelstiel (1956) who considered that fully developed nephrons should be absent from the septa of the cyst. Although these principles are considered to be of value, there are cases of bilateral multilocular cysts or of 2 multilocular cysts in one kidney.

Histologically, multilocular cysts are formed by multiple cavities lined by epithelium and surrounded by fibromuscular stroma or by undifferentiated metanephric stroma with or without glomerulotubular differentiation (Uson *et al.*, 1960; Christ, 1967; Fowler, 1971). In some cases the presence of undifferentiated metanephric stroma had suggested a close relationship between the genesis of multilocular cysts and Wilms' tumour, and some multilocular cysts have therefore been reported under the name of cystic nephroblastoma.

The present paper describes a case of multilocular cyst with a papillary and adenomatous malignant transformation of its epithelial lining. Its histogenesis and possible relationship with Wilms' tumour will also be discussed.

Case Report

The patient, a 65-year-old female of pykinc build, had

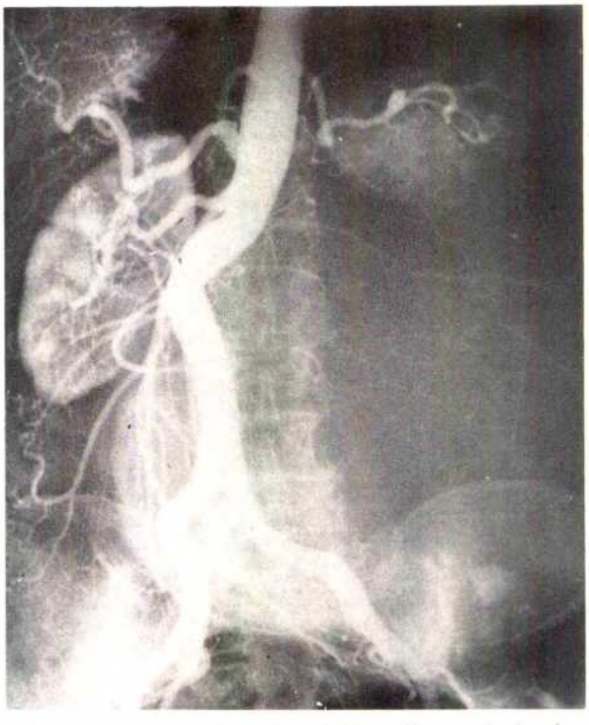

Fig. 1 Selective arteriography of the coeliac trunk showing the displacement of the aorta by a poorly vascularised abdominal mass on the left side. Over this mass the splenic artery and the spleen shadow can be seen.

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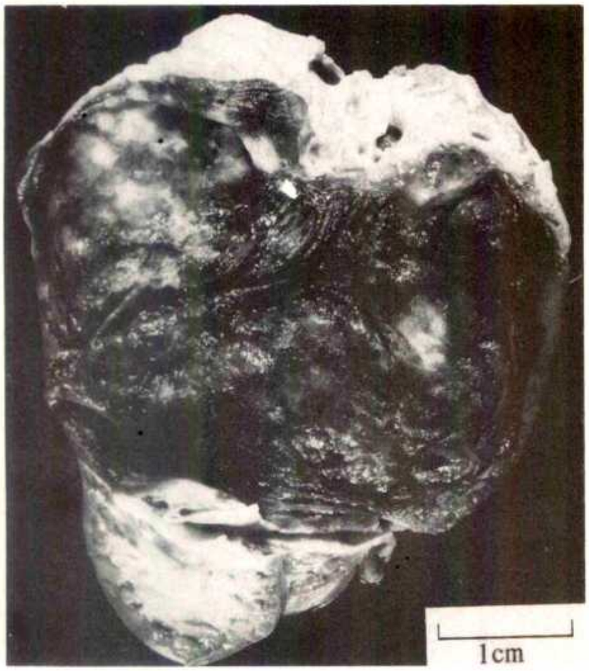

Fig. 2 Section of the left kidney showing the main cyst and the multiple cystic cavities with a honeycomb appearance in the upper pole.

no relevant personal or family history. Three months earlier, after a slimming cure, she had discovered a mass in the hypochondrium and left flank with no other symptomatology.

Analytical data were normal, except for a strongly positive Casoni reaction.

On examination a solid mass was found in the hypochrondrium and left flank extending beyond the middle line. Plain X-ray of the abdomen, barium meal and enema showed displacement of the small intestine to the right and of the stomach towards the front; the transverse and descending colon were also displaced. In the excretion urogram the right renal pelvis, the final portion of both ureters and the urinary bladder were seen, but not the left kidney.

Scintigraphy of the kidneys showed no uptake of isotope on the left side. The right kidney was normal. Arteriography (Fig. 1) showed lateral displacement of the abdominal aorta, a normally vascularised right kidney and a poorly vascularised abdominal mass possibly consistent with a cystic tumour in the area of the left kidney.

The pre-operative diagnosis was cystic tumour of the left kidney, the strongly positive Casoni reaction suggesting a hydatid cyst.

A laparotomy was performed. When the peritoneum was opened a mass (the size of a fetal head) could be seen in the retroperitoneal area, below the left mesocolon, with rounded margins and a cystic consistency. The left paracolic space was opened to isolate the tumour, which was found to be included in the renal parenchyma. A left nephrectomy with ureterectomy was performed.

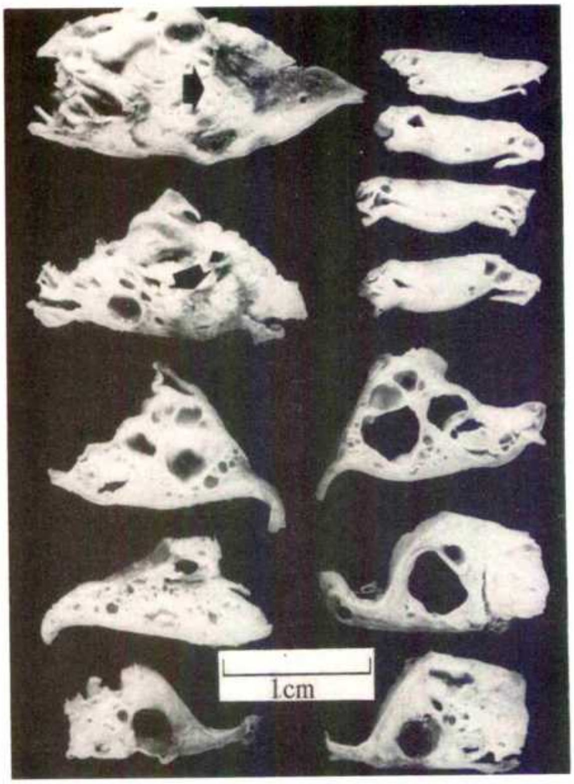

Fig. 3 Multiple sections of the upper pole. The arrow indicates the necrotic area which was macroscopically identified.

The specimen, which weighed 3 kg, consisted of a large cystic tumour of the left kidney, measuring 330 × 220 × 150 mm. On section the main cystic cavity contained dark brown fluid, but at the periphery there were multiple cavities or locules resembling a honeycomb and containing clear fluid (Fig. 2).

In one of these cystic areas, near the capsule, there was a yellowish necrotic zone approximately 15 × 10 × 5 mm (Fig. 3). Near the pelvis the tumour was solid and herniated into the pelvis, reaching the pyeloureteric junction (Fig. 4); it was similar to the tumour reported by Uson and Melicow (1963).

The rest of the pelvis was hydronephrotic. The inferior renal pole was normal, apart from some small retention cysts.

Microscopically, the polycystic area consisted of multiple cavities lined by flat columnar epithelium, with nuclear pseudostratification and papillary infoldings (Fig. 5). Other areas contained solid cells, sometimes with a central cavitation, especially near the pelvis (Fig. 6). The sparsely cellular stroma consisted of fusiform cells, collagen bundles, bands of smooth muscle and oedema. No undifferentiated metanephric blastema was found. In the cystic septa no mature nephrons

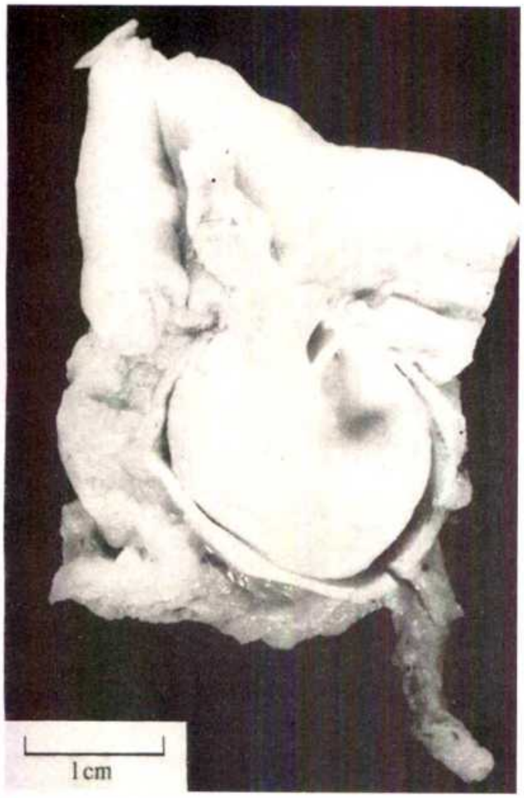

Fig. 4 Solid portion of the multilocular cyst herniated through the pelvis.

could be identified and no direct connection was found between cysts and renal pelvis.

The necrotic area described macroscopically showed a solid and papillary adenomatous proliferation, covered by columnar epithelium, either in a single layer or having a pseudostratified arrangement, areas of squamous, transitional cell and glandular differentiation forming solid sheets of cells which infiltrated the stroma. This proliferation continued into the benign cystic areas without transition (Fig. 7). The undamaged renal parenchyma showed a certain degree of pressure atrophy and the presence of small retention cysts. The diagnosis was papillary adenocarcinoma in a multilocular renal cyst in an adult.

Discussion

Some authors consider that multilocular cysts result from an abnormal development of the metanephric blastema and, therefore, are similar or identical to Wilms' tumour (Uson *et al.*, 1960; Christ, 1967; Fowler, 1971).

Fowler accepts that the only difference between Wilms' tumour and multilocular cyst is the maturity of the epithelium and stroma and the small proportion of undifferentiated neoplastic elements present.

The maturity of the components in our case was complete; the cysts were covered by columnar and pseudostratified epithelium with a mature fibromuscular stroma in which some solid nests of epithelial cells were found.

Others (Uson *et al.*, 1960) consider the multilocular cysts synonymous with cystic Wilms' tumour, especially when undifferentiated metanephric blastema dominates the histological picture.

However, it must be remembered that multilocular cysts, unlike nephroblastoma, are found in adults in 50% of cases (Kissane and Smith, 1967; Baldauf and Schulz, 1976) and that, unlike Wilms' tumours, they do not behave aggressively.

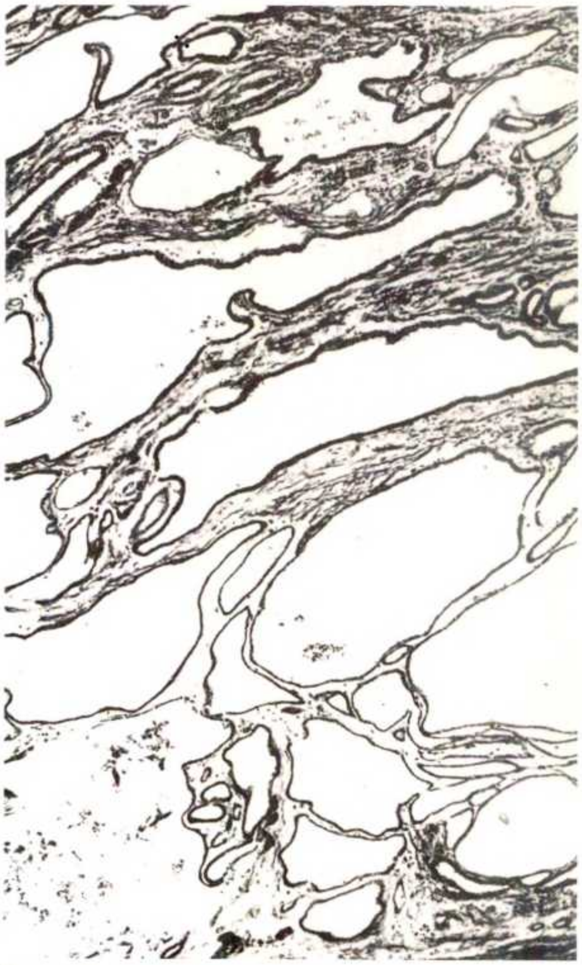

Fig. 5 This honeycomb area corresponds on histological examination to a benign cystic-papillary picture of a multilocular cyst (H and E ×40).

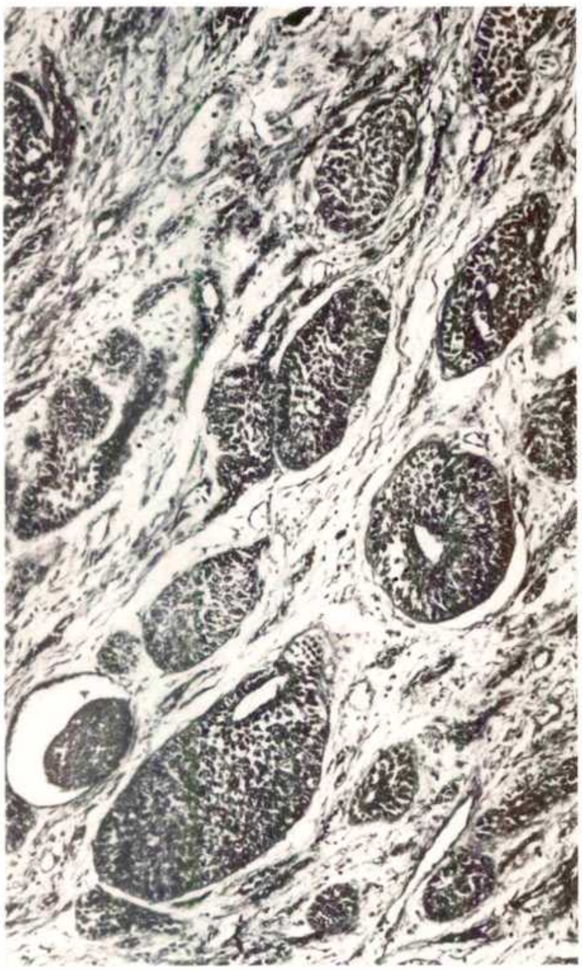

Fig. 6 Detail of this area showing the solid epithelial nests in a fibromuscular stroma (H and E ×160).

These facts lead us to consider multilocular cysts as a dysgenetic anomaly of the metanephric blastema and of the mesoderm included in the renal blastema, a true hamartomatous lesion as proposed by Arey (1959).

Although these tumours generally behave as benign tumours, focal malignant transformation is not excluded. The epithelial component may proliferate, forming a clear cell carcinoma or a papillary adenocarcinoma, as in the present case, whereas the areas of undifferentiated metanephric blastema may behave aggressively and develop into a true malignant Wilms' tumour.

In the published cases of multilocular cysts containing a renal cell tumour, no specific mention has been made of any direct transition between the cyst epithelium and the adenocarcinomatous area. Thus, it is not known if these lesions are only coincidental (Posso *et al.*, 1973) or if tumour cells arise in the epithelial lining of the cysts. In the present case, however, all degrees of transition between the cystic lining and the papillary adenocarcinoma were detected.

From the above discussion, the main problem would be whether to consider the areas of undifferentiated metanephric blastema as an habitual and benign component of the multilocular cyst or as a malignant element diagnostic of Wilms' tumour and therefore responsive to radiotherapy. In fact the small number of cystic nephroblastomas reported (Landing, 1958; Uson *et al.*, 1960; Boggs *et al.*, 1965; Christ, 1967; Fowler, 1971; Behr and Duari, 1975; Datnow and Daniel, 1976) do not show recurrence even without radiotherapy. For this reason some authors have suggested that

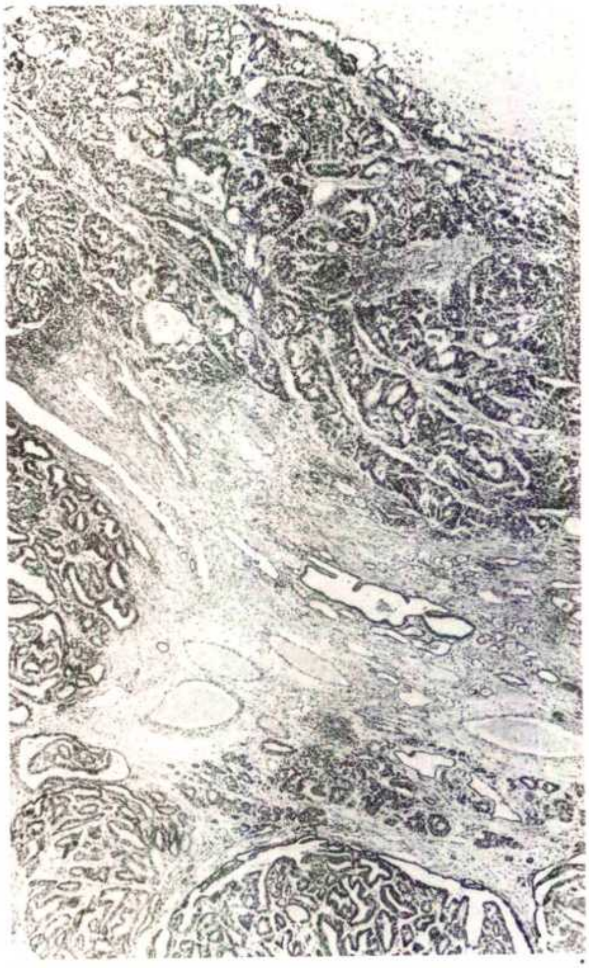

Fig. 7 Histological detail of the necrotic area, showing the solid adenocarcinomatous proliferation which continues with the benign cystic area (H and E ×4).

multilocular cysts should always be treated as benign neoplasms (Aterman *et al.*, 1973), but perhaps an exception should be made in cases associated with tumours or those in which papillary adenocarcinoma has developed.

In the present case a limited extension of the adenocarcinomatous area and its situation within the cyst, which had an intact capsule, allowed us to consider the surgical treatment as curative.

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Use of the Surgical Staple for Bowel Anastomoses in Urology

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Summary—The use of the Autosuture* stapling devices for performing enteric anastomoses is described. Such anastomoses can be performed more quickly and more uniformly than sutured ones, with few complications.

Diversion, bypass and augmentation of the urinary tract using an isolated segment of intestine are now commonplace in the repertoire of the urologist. The use of the Autosuture stapler is reported.

Materials and Methods

Bowel anastomoses using Autosuture staples were performed consecutively on 35 patients undergoing urinary diversion for pelvic carcinoma (bladder, cervix and rectum) and meningomyelocele. Sigmoid colon was used in 9 cases, transverse colon in 2 and in 24 cases terminal ileum was used. Four patients had previously received a full course of irradiation (7000 rads). Two of these 4 underwent transverse colon conduit to avoid irradiated tissue. The age range was from 4 to 76 years. Two types of anastomosis were used. For the colon an end-to-end anastomosis was created using a triangulation technique with the TA-55 -3.5 stapling device (Fig. 1). For the ileum a functional end-to-end anastomosis was created by anastomosing the bowel segments in a side-to-side fashion with the GIA stapler (Fig. 2). The TA-55 -3.5 stapler was used to close the common end. No reinforcing sutures were needed. Nasogastric suction was maintained for at least 72 h in all patients. Gastrostomy was used in 12 patients undergoing simultaneous cystectomy or anterior exenteration.

Details of the technique have been published previously and are available in a well-illustrated manual (*Stapling Techniques in General Surgery*, 1974).

Results

All 35 patients survived the procedure and there were no enteric leaks. Two cases of prolonged ileus were noted (greater than 7 days), but most observers felt that bowel function returned more quickly with stapled anastomoses than with conventional techniques. One anastomosis had mild bleeding at the edge after the GIA stapler had restored the lumina. The bleeding was easily controlled with a mattress suture, taking care to avoid the staple line. One episode of bowel obstruction occurred on the tenth post-operative day. Re-exploration revealed an internal hernia unrelated to the bowel anastomosis.

Discussion

Enteric anastomoses using sutures have been perfected over 150 years (Getzen, 1969a). One-layer and 2-layer anastomoses using silk, gut and synthetic materials have been used with predictable results. Problems with sutured anastomoses can and do occur from improperly placed sutures resulting in obstruction, bleeding or leakage (Getzen, 1969b). Bowel staples have been used for 25 years and have been modified and perfected by the United States Surgical Corporation. The use of staples for enteric anastomoses has been frequently described in the general surgical literature (Ravitch and Rivarola, 1966; Steichen, 1968). Articles have also appeared in the urological literature but few urologists use the technique (Johnson and Fuerst, 1973).

* United States Surgical Corporation, New York.

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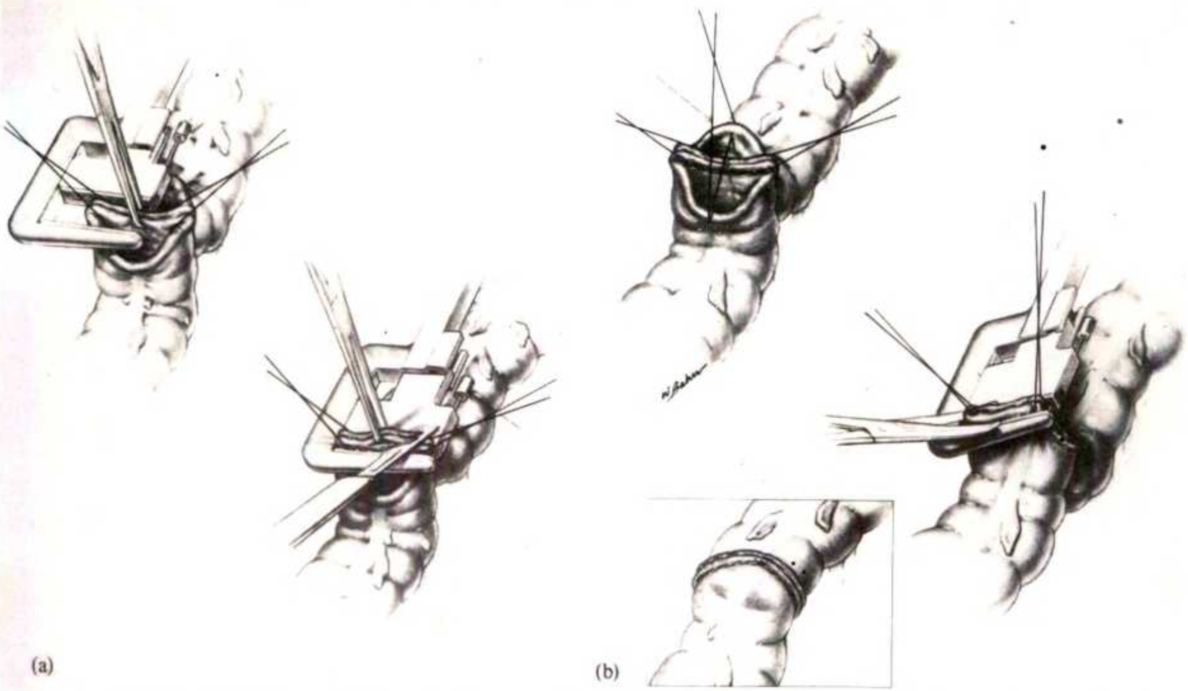

Fig. 1 (a) Using the principle of triangulation, the mesenteric third of the bowel lumen is joined by a double row of staples using the TA-55 -3.5. Extraneous tissue is excised by cutting between the rows of staples. (b) The antimesenteric two-thirds of the bowel lumen is divided in half and each area closed with a double row of staples. A direct end-to-end anastomosis has been created (see inset).

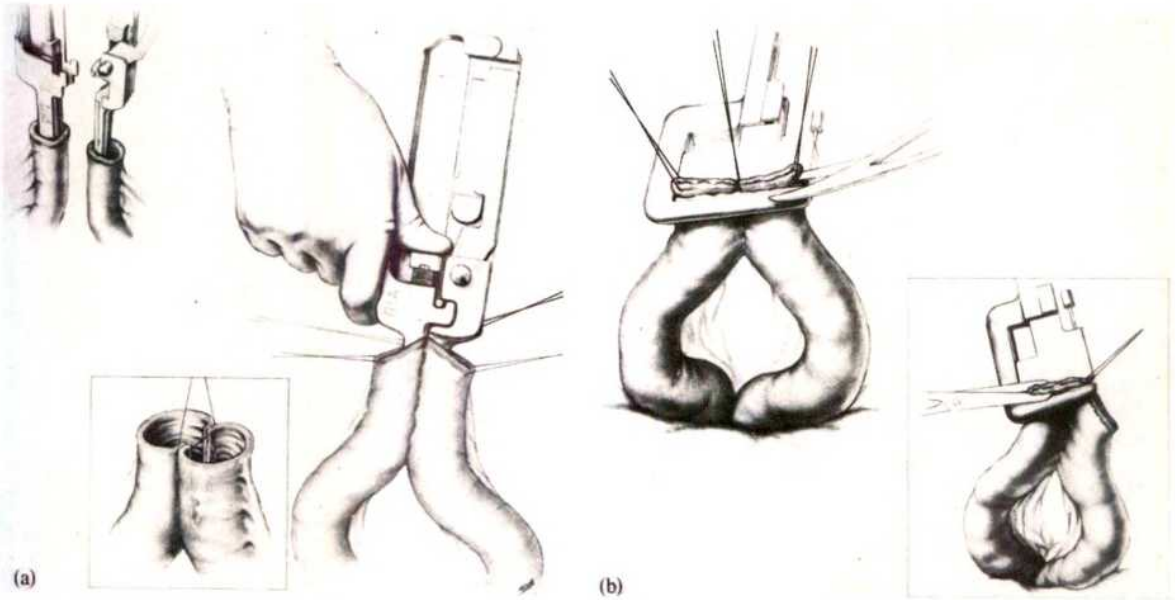

Fig. 2 (a) The GIA stapling device is opened and inserted into the opened lumina of the bowel. The device is then locked and the staples fired. The GIA is disengaged, leaving a side-to-side anastomosis with a double row of staples (see inset). (b) The open lumen is closed transversely with a double row of staples. This may be done in one or 2 steps (see inset). (c) The functional end-to-end anastomosis is completed and the mesentery closed. (Figure 2 continued on p. 20.)

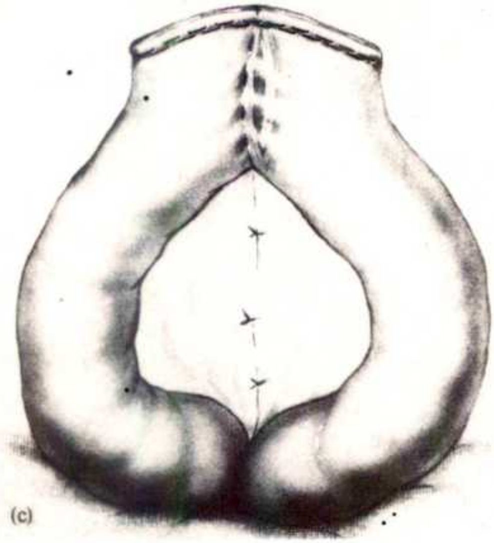

Fig. 2—*continued*

With Autosuture staples, the anastomosis of small bowel takes less than 5 min and is uniform in all instances. An end-to-end anastomosis for large bowel takes about 10 min and is easily performed. In addition, less clearing of the mesenteric border is needed, thus saving surgical time and reducing the incidence of mesenteric vessel injury and subsequent haematoma formation. Malfunction of the equipment is infrequent provided that the prescribed techniques are followed. Closure of the urinary conduit with staples is somewhat controversial because of possible stone formation (Assadnia *et al.*, 1972). Conduit closure has been performed in 6 patients with follow-up lasting from one to 9 months. To date no stone formation has been reported. Operative time for conduit closure is 30 s.

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The Effect of Exogenous Prostaglandins $F_{2\alpha}$ and E_2 and Indomethacin on Micturition

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Summary—The influence of exogenous infusion of prostaglandins (PGs) of the $F_{2\alpha}$ and E_2 series and of indomethacin on micturition cycles was investigated in 30 anaesthetised female dogs. In 30 other animals, urethrovesical disconnection was performed to study the action of PGs and of indomethacin without the muscle continuity factors.

In the intact animal model during vesical distension, PGE_2 produced a significant urethral pressure drop and a dose-dependent reduction in the threshold micturition volume. $PGF_{2\alpha}$ produced a significant urethral pressure rise. At doses higher than 0.3 μg/kg, $PGF_{2\alpha}$ reduced the threshold micturition volume. On the other hand, indomethacin significantly increased the threshold micturition volume and reduced the maximum intravesical pressure.

In the disconnected model, PGE_2 produced a dose-dependent decrease in the resting urethral pressure and hardly affected the intravesical pressure; $PGF_{2\alpha}$ produced a dose-dependent increase in both urethral and intravesical pressures.

Thus it is suggested that endogenous PG release during vesical distension could play a facilitatory role in micturition.

Prostaglandins were shown to be liberated into the bloodstream of dogs during vesical distension (Gilmore and Vane, 1971; Ghoneim *et al.*, 1976; Khalaf *et al.*, 1979) and after pelvic nerve stimulation (Khalaf *et al.*, 1979). Similarly, PG-like material was detected in bladder washout effluent collected after micturition and pelvic nerve stimulation (Khalaf *et al.*, 1980). Since exogenous PGs produce profound changes in the vesical (Taira, 1974; Bultitude *et al.*, 1976) and urethral (Ghoneim *et al.*, 1976; Andersson *et al.*, 1977) muscles, it was suggested that endogenous PGs could play a role in vesicourethral function.

To test this hypothesis we studied the influence of exogenous PGs as well as indomethacin on some micturition parameters.

Materials and Methods

Animal Preparation and Experimental Design

Female non-pregnant mongrel dogs (9-21 kg weight) were anaesthetised with intravenous α-chloralose-urethane solution (100 and 500 mg/kg respectively) in saline. Stable light anaesthesia was maintained by intravenous infusion of 1 ml of 0.4% α-chloralose solution per min throughout the duration of the experiment. After endotracheal intubation the respiration was mechanically controlled by a pump with an oxygen flow of 2 l/min. Following episiotomy the bladder was exposed through an abdominal incision and 2 polyethylene tubes were inserted through the dome into its cavity—one to record the intravesical pressure and the other to fill and empty the bladder. Both ureters were divided above the bladder and the urine was diverted to the exterior by 2 polyethylene tubes to maintain bladder volume by external infusion only. Both femoral arteries were cannulated and the catheters were guided to lie at the aortic bifurcation (Fig. 1). One catheter was used to record blood pressure changes and the other to infuse prostaglandin solution and Urecholine (Burroughs Wellcome). The urethral pressure was measured by the 2 membrane chambers of a multichannel membrane catheter (Heyer-Schulte Corporation, California). The membrane chamber (U_1) was positioned in the proximal half of the urethra at the site of maximum pressure and the other chamber (U_2) laid 1 cm distal to U_1. The catheter was secured in position by a stitch placed near the external meatus. A balloon rectal catheter was used to measure the rectal pressure as a

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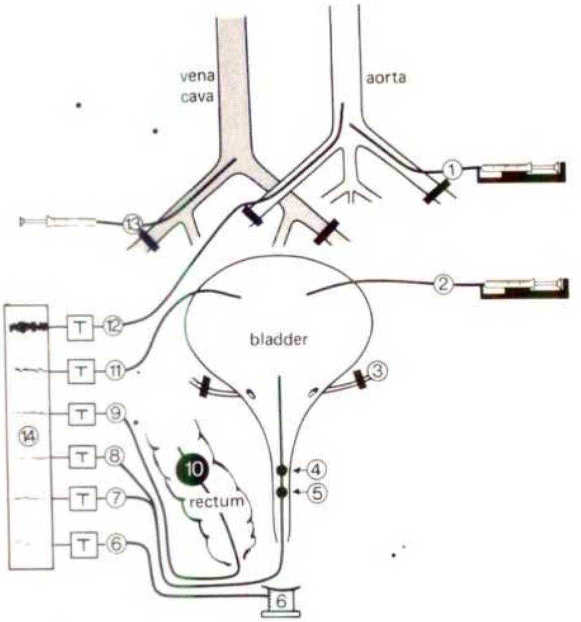

Fig. 1 Diagram of the experimental design and recording system. Drugs are infused into the arterial cannula (1). Bladder is filled from a pump (2) to induce micturition cycles. Ureters are divided and ligated (3). Urethral pressure is measured by 2 membrane chambers (4, 5). Venous cannula (13). Pressure measuring catheters and flow (4-12) are connected to transducers (T) that are coupled to a pen-recorder (14).

monitor of the intra-abdominal pressure. Urinary flow was measured by a flowmeter based on the principle of air displacement (model UF-2, Physico-Medical System Corporation, Montreal). Because of the presence of a catheter in the urethra, flowmetry was used only to indicate the timing of the flow in relation to other parameters in the voiding cycle. Pressure measuring catheters were connected to Statham pressure transducers (P_{23} De) which, together with the flow sensor, were coupled to a multichannel ink-writing pen recorder (Model 2500, Honeywell Corporation, Colorado). A diagram of the experimental design is shown in Figure 1.

Experimental Protocol

Control voiding cycles were obtained by constant slow bladder filling with saline from a pump (4-8 ml saline/min at room temperature). When a critical degree of bladder filling was reached (threshold volume of micturition), reflex detrusor contraction occurred and micturition followed. Voiding cycles were repeated until reproducibility was assured as evidenced by constant threshold micturition volume and constant pattern of urethrovesical pressure changes. The following experiments were done to study the effect of PGs and PG-synthetase inhibitor indomethacin on micturition parameters. In every experiment each animal acted as its own control in depicting a change in the urodynamic parameters following drug injection or pelvic nerve stimulation.

A. Influence of Intra-arterial PGs Infusion

The effects of intra-arterial administration of PGs of the E_2 and $F_{2}\alpha$ series on some urodynamic voiding parameters were investigated in 42 dogs of 2 different experimental models:

1. Intact Model Group In 20 animals an intact model was used as shown in Figure 1. PGs were infused while the bladder was slowly filled with

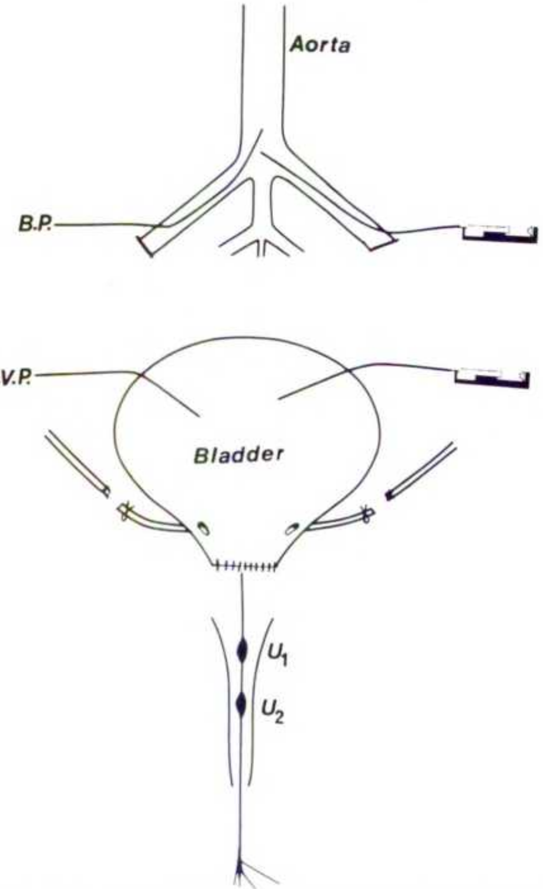

Fig. 2 Vesicourethral disconnection model used to study the resting intravesical pressure (IVP) and urethral pressure (U_1 and U_2) changes in response to intra-arterial prostaglandin infusion or Urecholine. The bladder contained a constant volume and both ureters are divided to drain urine to the outside.

saline. In these experiments the influence of PGs on the integrated urethrovesical function was studied. The changes in the threshold volume of micturition and the maximum intravesical and urethral pressures were observed.

2. Vesicourethral Disconnection Group In 22 other animals complete vesicourethral interruption at the level of the bladder outlet was performed to exclude direct transmission of muscle action and/or hydraulic factors between the bladder and urethra (Fig. 2). The bladder was filled to half of its threshold volume with saline. This volume was kept constant throughout the experiment to study the influence of different concentrations of PGs on the resting intravesical and urethral pressures.

Freshly prepared prostaglandin solutions were used. Prostaglandin E_2 was dissolved in absolute ethanol (1 mg/ml), while $PGF_{2\alpha}$ was dissolved in distilled water (1 mg/ml). Appropriate dilutions of both PGs were made in saline. After animal preparation, saline was infused intra-arterially by a pump at a constant rate of 1 ml/min. After assuring reproducibility of the measured urodynamic parameters, PGE_2 and $PGF_{2\alpha}$ in saline were individually infused at the same rate (1 ml/min) to deliver the following dose concentrations at the aortic bifurcation: 0.03, 0.1, 0.3, 1.0 and 3 μg/kg/min. Each concentration was given for nearly equal periods of time in each experiment. The relationship between each concentration of the prostaglandins and the mean changes in each urodynamic parameter was plotted against the different PG concentrations used to give several dose response curves.

B. Influence of Indomethacin

Indomethacin (Merck, Sharp and Dohme), freshly prepared for each experiment, was dissolved in 0.2 M Trizma HCl (Sigma). The solution was given intravenously at a dose of 12 mg/kg to 18 dogs in 2 sets of experiments:

1. Intact Model Group (voiding cycle experiments) Indomethacin effects on micturition cycles were studied in 10 dogs. Control micturition cycles were obtained 3 times before indomethacin administration, following which 3 other cycles were recorded 30 min later. In each experiment the parameters evaluated in the micturition cycles were calculated as the mean of 3 cycles done either before or after indomethacin. In 3 animals of the same group, Trizma solution was injected intravenously to examine a possible action of the solvent.

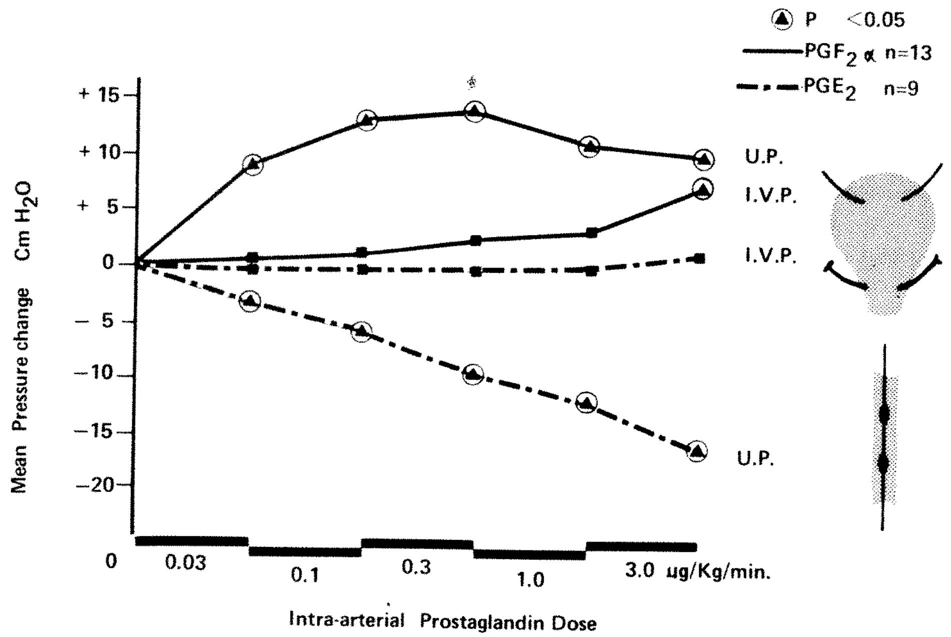

Fig. 3 Dose-response curve for the resting urethral pressure (UP) and resting intravesical pressure (IVP) to intra-arterial $PGF_{2\alpha}$ and PGE_2. Each value represents the mean pressure change from control before PG infusion, *i.e.* control value = 0. Circled triangles indicate values significantly ($P =$ or <0.05) different from control.

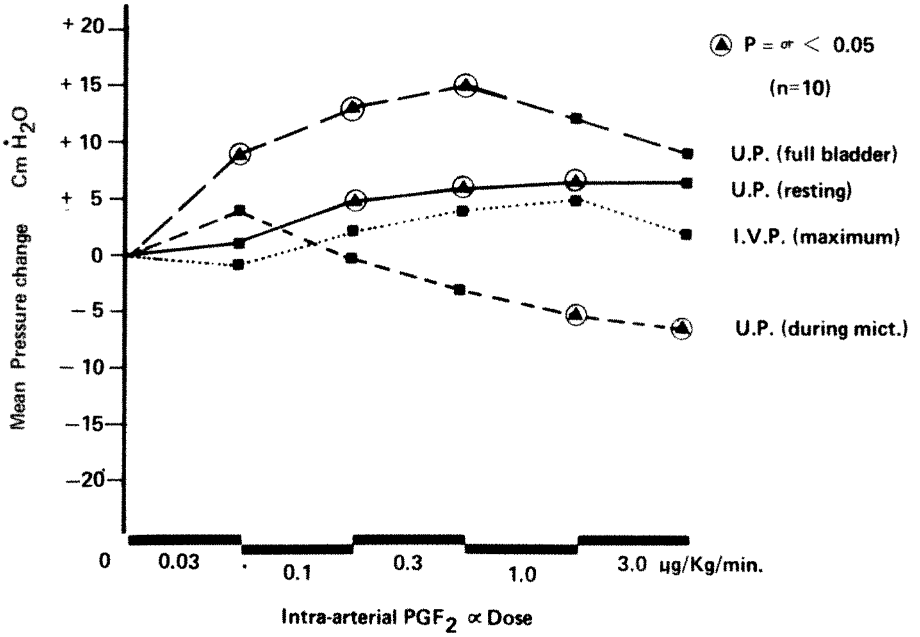

Fig. 4 Dose-response curve for pressure changes in the urethral pressure (UP) and intravesical pressure (IVP) to $PGF_{2}\alpha$ intra-arterial infusion. Each value is the mean result from 10 animals. At the 1 to 3 μg/kg doses there is a significant drop in UP (during micturition) despite insignificant changes in IVP (maximum). Before micturition the UP (full bladder) also showed a relative drop during the same doses. Circled triangles represent significant values from control.

2. *Vesicourethral Disconnection Group* In 8 other animals the disconnection model described above (Fig. 2) was used to examine the influence of indomethacin on pelvic nerve-induced and Urecholine-induced bladder contraction. The bladder was filled to half of its threshold volume with saline and this volume was kept constant throughout the experiment so as to get an isometric contraction. One intact pelvic nerve was stimulated (5 experiments) with electrical pulses of 15 V and 0.2 ms duration at a frequency of 20 Hz for 2 s from a Grass stimulator (Model S4K). Urecholine was given intra-arterially in a dose of 30 μg in 3 experiments. The isometric detrusor contraction (induced either by pelvic nerve stimulation or by Urecholine) was obtained twice before and twice after indomethacin. Changes in the amplitude of isometric detrusor contraction before and after the use of indomethacin were noted.

Statistical Analysis of Data

Each animal acted as its own control in calculating a change in any measured parameter. Each control value was considered as "unity". The degree of change was calculated to compute a mean change or a mean value at the different experimental points. Dose-effect data were analysed by Fischer's analysis of variance. Difference between the means of any value and its corresponding control was analysed by Student's t-test for paired values. A "*P*" value of 0.05 or less ($P<0.05$) was chosen for statistical significance.

Results

A. Influence of intra-arterial $PGF_{2}\alpha$ and PGE_2

1. Intact Model Group

The maximum intravesical pressure showed insignificant changes during intra-arterial infusion of $PGF_{2}\alpha$ (Fig. 3) or PGE_2 (Fig. 4).

Urethral Pressure (UP) The resting urethral pressure (recorded between the micturition cycles) showed a gradual dose-dependent increase during $PGF_{2}\alpha$ infusion (Table 1 and Fig. 4). On the other hand, PGE_2 produced insignificant changes in the resting urethral pressure (Table 2 and Fig. 5).

During bladder filling, PG infusion caused urethral pressure changes that differed from those of control cycles. Prostaglandin $F_{2}\alpha$ produced a

Table 1 Influence of $PGF_{2}\alpha$ on some Urodynamic Voiding Parameters*

	Control		*Intra-arterial $PGF_{2}\alpha$ dose (μg/kg/min)*				*P*‡
	0.0	*0.03*	*0.1*	*0.3*	*1.0*	*3.0*	
Maximum intravesical pressure	28	27.2±1.5	30.2±2.3	31.9±2.8	33.0±3.8	30.2±3.9	0.6
Urethral pressure, resting	38.5	39.8±0.9	43.4±1.5†	44.3±1.8†	44.7±2.5†	44.7±3.0†	0.1
Urethral pressure, full bladder	47.4	56.3±2.6†	60.6±3.7†	62.1±4.8†	59.5±6.6	56.9±4.7	0.2
Urethral pressure, micturating	29.5	33.9±4.6	29.8±2.3	26.2±2.3	24.7±2.7†	23.6±2.2†	0.1
Threshold micturition volume (ml)	66.9	66.2±2.6	61.4±4.1	58.9±5.4	53.5±6.2†	51.5±4.6†	0.09

* Mean ± SEM values of 10 experiments. Pressure values are expressed in cmH_2O.

† A significant difference exists between values marked by dagger and their corresponding control as assessed by Student's t-test for paired values ($P<0.05$).

‡ Associated probability for Fischer's analysis of variance; $P<0.05$ is the level of significance.

significant dose-dependent urethral pressure rise up to the 0.3 μg/kg dose, after which an insignificant pressure rise was observed. During micturition, a tendency for the urethral pressure to drop was observed following the infusion of $PGF_{2}\alpha$ in doses of 0.3 μg or higher. This urethral pressure drop during micturition with $PGF_{2}\alpha$ was significantly different from control values at the 1 and 3 μg doses (Fig. 4, Table 1). On the other hand, PGE_2 produced a significant urethral pressure drop at full bladder and during micturition. This effect was observed from the 0.3 μg dose and higher (Fig. 5, Table 2).

Threshold Micturition Volume PGE_2 produced a significant dose-dependent reduction in the threshold volume of micturition (Fig. 6). On the other hand, $PGF_{2}\alpha$ produced an insignificant reduction in the threshold volume except when the high concentrations of 1 and 3 μg/kg/min were used (Table 1).

2. *Disconnected Model Experiments* (Fig. 3)

Intravesical pressure (IVP): prostaglandin $F_{2}\alpha$ infusion in increasing doses caused a gradual rise of the resting intravesical pressure to reach a significant level at the 3 μg/kg dose (Fig. 3). On the other hand, no change could be observed following PGE_2 infusion at all concentrations (Fig. 3).

The resting urethral pressure showed a significant dose-dependent drop during PGE_2 infusion. On the contrary, $PGF_{2}\alpha$ infusion produced a dose-dependent rise up to the 0.3 μg/kg dose, after which the increase was less pronounced.

B. Influence of indomethacin

1. *Intact Model Group*

Indomethacin produced a significant increase in the threshold volume of micturition. Moreover, a significant reduction of the maximum intravesical pressure was also observed (Table 3). The intravenously administered indomethacin solvent (Trizma HCl in a dose of 4 ml of 0.2 M solution/kg) had virtually no effect on the micturition cycles.

Table 2 Influence of PGE_2 on some Urodynamic Voiding Parameters*

	Control		*Intra-arterial PGE_2 dose (μg/kg/min)*				*P*‡
	0.0	*0.03*	*0.1*	*0.3*	*1.0*	*3.0*	
Maximum intravesical pressure	36.8	38.3±1.6	39.4±3.7	34.6±3.1	35.7±3.2	36.8±4.2	0.8
Urethral pressure, resting	42.6	42.6±1.3	40.5±1.9	40.5±3.4	37.8±3.5	35.6±4.1	0.4
Urethral pressure, full bladder	43.1	41.7±1.5	41.0±2.1	35.6±2.3†	27.0±1.5†	25.5±1.9†	0.001
Urethral pressure, micturating	25.0	24.8±2.6	23.5±2.1	22.5±1.5	21.0±2.1†	18.1±2.6†	0.04
Threshold micturition volume (ml)	77.6	63.0±3.6†	50.4±5.4†	45.6±3.4†	36.7±3.4†	32.0±5.3†	<0.0001

* Mean ± SEM values of 10 experiments. Pressure values are expressed in cmH_2O.

† A significant difference exists between values marked by dagger and their corresponding control as assessed by Student's t-test for paired values ($P<0.05$).

‡ Associated probability for Fischer's analysis of variance; $P<0.05$ is the level of significance.

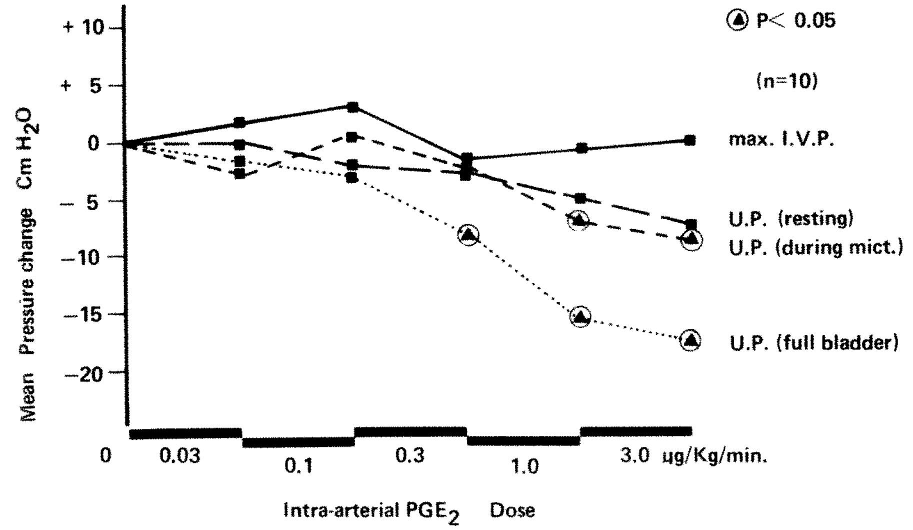

Fig. 5 Dose-response curve for urethral (UP) and intravesical (IVP) pressure changes to PGE_2. Each value is the mean result for 10 animals. A significant reduction in urethral pressure during filling and micturition is observed at the right half of the curve.

2. *Disconnected Model Experiments*

Indomethacin in the administered doses produced no significant change in the amplitude of isometric detrusor contraction in response to repeated doses of bethanechol chloride. Nevertheless, indomethacin produced a significant reduction in the amplitude of isometric detrusor contraction following pelvic nerve stimulation (Table 4).

Discussion

In the present work the *in vivo* effects of exogenous $PGF_2\alpha$ and PGE_2 on the vesicourethral functions were examined in 2 models. One model allowed for the simultaneous separate recording of the intravesical and urethral pressures with elimination of the possible effects of muscle continuity and/or hydraulic factors. The other model

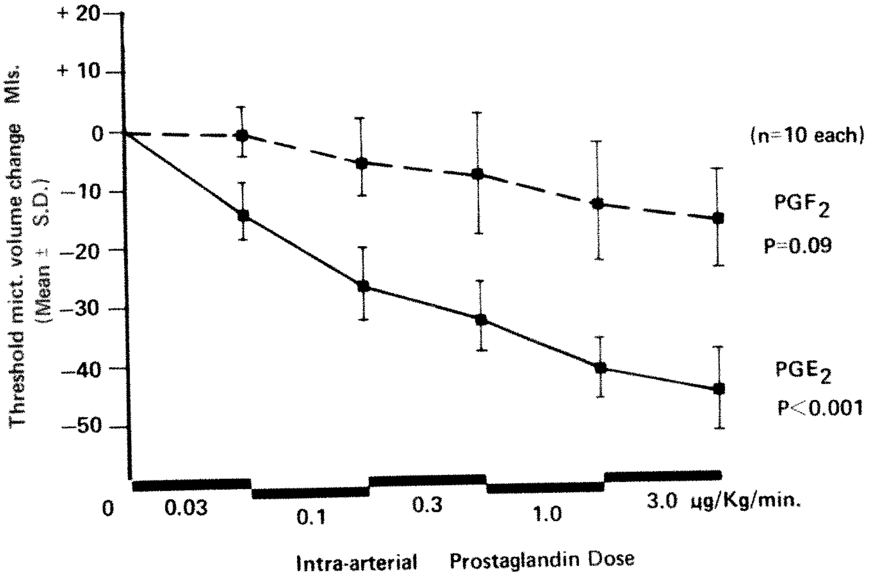

Fig. 6 Dose-response curve of the threshold micturition volume to intra-arterial PGE_2 and $PGF_2\alpha$. Each value is the mean change SD of 10 experiments from the control. Fischer's analysis of variance showed highly significant ($P<0.0001$) reduction during PGE_2 infusion.

Table 3 Influence of Indomethacin on some Urodynamic Voiding Parameters*

	Control	*Indomethacin*	*P*†
Maximum intravesical pressure	36.1±3.5	31.3±3.5	0.01
Urethral pressure, resting	48.2±5.5	40.9±5.4	0.08
Threshold micturition volume (ml)	114.9±17.0	155.2±25.2	<0.001

* Mean ± SEM values of 10 experiments. † Student's t-test. Significant $P<0.05$.

permitted the study of the effect of PGs on the integrated vesicourethral function during both phases of the micturition cycle: filling and expulsion.

The intravesical pressure showed insignificant changes during intra-arterial PG infusion except with high doses of PGF$_{2\alpha}$ in the disconnected model, where a pressure rise was observed. Prostaglandins of the F$_{2\alpha}$ and E$_2$ series were reported to produce sluggish contractions of detrusor strips of human and animal species (Ambache and Zar, 1970; Bultitude *et al.*, 1976; Andersson *et al.*, 1977). Taira (1974) demonstrated that a single injection of PGF$_{2\alpha}$ at the doses 10 to 100 μg into the caudal vesical arteries in the dog produced a slowly developing sustained increase in bladder tone.

Under resting bladder conditions PGs produced changes in the urethral pressure that were more evident in the disconnected model. Prostaglandin E$_2$ produced a dose-dependent reduction in urethral pressure in the disconnected model and insignificant changes in the intact model. On the other hand, PGF$_{2\alpha}$ produced a dose-dependent rise in the resting urethral pressure in both the disconnected and intact models. Nevertheless, at the high doses of 1 to 3 μg/kg, PGF$_{2\alpha}$ produced a detrusor contraction and induced a urethral pressure drop in the disconnection model. This pressure drop can possibly be explained by a reflex mechanism consequent to detrusor contraction.

The difference in the vesicourethral responses between the 2 models to PG infusion can be explained, not by animal variations, but by the muscle continuity between the bladder and urethra transmitting pressure changes from one part of the muscle to the other. Accordingly the influence of exogenous PG on the urethral pressure in the intact model represents a summation of its direct effects on the urethra added to the transmitted tonic responses on the detrusor muscle and its urethral continuation. This can explain why the inhibitory effect of PGE$_2$ on the urethra of the intact model is not as evident as in the disconnected model. In this context PGE$_2$ was reported to produce dose-dependent excitatory responses on the longitudinal and inhibitory effects on the circular muscles of the stomach and ileum (Bennett *et al.*, 1968). This mode of action, if applied to the vesicourethral muscles, may explain the different urethral pressure responses to PGE$_2$ in the intact and disconnected models. Interruption of the longitudinal muscle continuity to the urethra at the bladder neck in the disconnection model probably reduces the transmitted pressure changes of this muscle on the urethral pressure.

Table 4 Effect of Indomethacin on Isometric Detrusor Contraction*

	N	*Control*	*Indo-methacin*	*P*†
Bethanechol chloride	3	36.3	38.1±1.9	0.49
Pelvic nerve stimulation	5	47.0	39.4±2.8	0.02

* Mean SEM. † Student's t-test.

The influence of PGE$_2$ on the urethra can be mediated either through a direct action on the smooth muscles of the urethra (Taira, 1974; Andersson *et al.*, 1977) or through their known inhibitory effects on the adrenergic transmission (Hedqvist, 1973). It is now well established that the canine resting urethral pressure is in part a function of α-adrenergic innervation (Raz and Caine, 1972).

Experiments involving the use of indomethacin for PG synthesis inhibition were conducted to provide further evidence of the possible rôle of PG in the physiology of voiding. Indomethacin produced opposite effects to those observed with exogenous PG on the vesicourethral function. The threshold micturition volume was increased and the maximum intravesical pressure reduced. Since indomethacin can produce its effects on the smooth muscles through either PG synthetase inhibition (Vane, 1971) or its known calcium antagonistic responses (Northhover, 1971), further experiments were conducted to test its effect on excitation contraction coupling in the bladder.

Evidence was provided that indomethacin action seemed to be mediated through PG synthesis inhibition as it did not modify agonist-induced detrusor contraction. Similarly, indomethacin was shown to produce no change in agonist-induced responses of detrusor strips of many animal species, while it partially inhibited detrusor responses to transmural stimulation in the presence of atropine (Choo and Mitchelson, 1977; Johns and Paton; 1977; Dean and Downie, 1978). Moreover, Eckinfels and Vane (1972) and Bultitude *et al.* (1976) found that indomethacin could depress the smooth muscle of the bladder in several species, an action that they suggested was due to PG-synthesis inhibition. It was suggested that prostaglandins were released during motor excitation of the detrusor in these animals and could contribute to the resultant contractile response.

The experimental data of this study collectively suggest that PGs are involved in the vesicourethral function and their rôle is to facilitate micturition. The fact that inhibition of PG synthesis increased the threshold micturition volume has provided evidence that prostaglandins may play a rôle in the physiology of voiding. Data on the pharmacological effects of PGs on the vesicourethral muscle have to be interpreted with caution, as far as their physiological significance is concerned, because of the high dose levels used. Nevertheless, a substantial release of PGs into the blood stream during micturition was demonstrated in a previous study in dogs (Khalaf *et al.*, 1979). Taken together, these findings add further support to the possible involvement of PGs in micturition.

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Incontinence Following Transurethral Resection of the Bladder Neck in the Female

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Summary—Incontinence is an unwelcome complication of transurethral resection (TUR) of the bladder neck in the female. A computerised analysis of 238 procedures performed during the period 1940 to 1972 was carried out to assess the morbidity due to this complication and to evaluate possible predisposing factors.

Initially 15.2% of patients were incontinent but 70% of these soon became continent without further treatment. The remaining 4.7% were treated by surgical or other measures. The incidence of incontinence was unrelated to the amount of tissue removed or to the number of operations, but was significantly lower when the operation was done for polypi of the bladder neck and significantly higher in patients with a cystocele or urethrocele. It seems possible to reduce the incidence of incontinence by careful selection of cases.

The fear of post-operative incontinence has made transurethral resection of the bladder neck in the female unpopular despite several reports which suggest that morbidity from incontinence after this procedure is reasonably low (Thompson, 1939; Emmett *et al.*, 1950; Nelson *et al.*, 1957). Either the incontinence rates quoted in the literature are too low or the fears generally held are too exaggerated. Incontinence may also follow other procedures suggested as alternatives to TUR of the bladder neck in the female (Keitzer *et al.*, 1961; Kerr *et al.*, 1966; Bonin, 1969), though Ray (1967), Pinard (1969) and Keitzer and Allen (1970) claim that transurethral incision (TUI) of the bladder neck reduces the incidence of incontinence. This study presents a detailed analysis of data pertaining to the occurrence of incontinence after TUR of the bladder neck in the female and attempts to identify predisposing factors.

Material and Methods

Two hundred and thirty-eight procedures carried out between 1940 and 1972 were studied (including those performed by residents under supervision). The length of follow-up extended to 5 years. The oldest patient was 85 years and the youngest 3 years old; 12 were under 10 years of age. In some patients more than one procedure was performed. The indications for surgery were bladder neck hypertrophy (collar contracture of bladder neck), polypi at the bladder neck and "to improve drainage" in the neurogenic bladder. Other procedures such as litholapaxy, removal of bladder tumours and resection of benign or Hunner's ulcer were performed together with transurethral resection of the bladder neck. The types of procedure included the standard TUR of the bladder neck with or without incision of the trigone, TUI of the bladder neck and TUR of the bladder neck polypi only. In some instances these procedures were combined. The technique was that described

Table 1 Incidence and Course of Various Types of Post-operative Incontinence

Type of incontinence	*Initially present*	*Post-operative course*	
		Persistent	*Spontaneously relieved*
Urgency	2	2	0
Stress	22	5	17
Urgency + stress	2	0	2
Constant leakage (without overflow)	10	5	5
Overflow	1	1	0
Type not stated (? mixed)	8	0	8
Total	45	13	32

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Table 2 Correlation Between Pre-operative and Post-operative Incontinence

Pre-operative incontinence		*Post-operative incontinence*		
		Absent	*Present initially*	*Persistent*
Present	(48)	32	16 (33%)	4 (8.8%)
Absent	(190)	161	29 (15.2%)	9 (4.7%)
Total	(238)	193	45	13

by Barnes *et al.* (1959). The instruments used were hot loop types, mainly the McCarthy resectoscope.

We studied the incidence, type and course of incontinence, and the effect upon these of such factors as pre-operative incontinence, the amount of tissue removed at surgery, the indications for surgery, the type and number of operations and the presence of cystocele and urethrocele.

The data (compiled with the aid of the Scientific Computation facility of Loma Linda University) were transferred to punch cards and analysed with the help of a computer. The significance of the differences between the incidences was tested by calculating the exact probability of a 2 × 2 contingency table.

Observations

Incidence, Types and Clinical Courses of Post-operative Incontinence

The incidence of various types of post-operative incontinence is shown in Table 1. Stress incontinence was present in 50% and constant leakage in 22%.

Initial post-operative incontinence (noted immediately after removal of the catheter) occurred in 45 out of 238 procedures (18.8%), but 16 of these were incontinent pre-operatively; therefore the true incidence of initial incontinence attributable to the procedure was 15.2% (29 out of 190 pre-operatively continent cases) (Table 2).

Table 3 Time Required for Spontaneous Relief of Incontinence

Time	*No. of procedures*
<1 month	2
<3 months	13
<6 months	4
<12 months	6
Exact time not stated (but <12 months)	7
Total	32

Table 4 Occurrence of Post-operative Incontinence in Relation to Indication for Surgery

Indication for surgery	*Incontinence*		*Total*
	Present	*Absent*	
1. Bladder neck hypertrophy	40	141	181
2. Polypi bladder neck	2	25	27
3. 1 and 2	2	15	17
4. Neurogenic bladder	1	5	6
5. 1 and 4	0	7	7
Total	45	193	238

Many of those initially incontinent were spontaneously and completely relieved over a 1 to 12-month period following the operation and most within 1 to 3 months (Table 3). The incidence of spontaneous relief was 32 out of 45 cases (70%). The incidence of spontaneous cures was lower in the group with constant leakage. In 13 instances incontinence was persistent; since 4 of these patients were incontinent pre-operatively the true incidence of persistent incontinence attributable to the procedure itself was 4.7%.

Further Management of Cases with Persistent Incontinence

One patient with constant leakage before and after operation suffered from an unidentified neurogenic disorder and died 3 months later from infection. One patient with urge incontinence before and after operation was partially relieved by psychotherapy and further surgery was not advised. Five patients, including 2 pre-operatively incontinent patients, refused further surgery be-

Table 5 Type of Incontinence in Relation to Indications for Surgery

Type of incontinence	*Indications* for surgery*			
	1	*2*	*3*	*4*
Urgency	2	0	0	0
Stress	19	1	2	0
Urgency + stress	3	0	0	0
Constant leakage	8	1	0	1
Not recorded	8	—	—	—
Total	40	2	2	1

* Indications:
1. Bladder neck hypertrophy.
2. Bladder neck polypi.
3. 1 and 2.
4. Neurogenic bladder.

cause their symptoms were not sufficiently severe. The 6 remaining patients (3 with stress incontinence and 3 with constant leakage) were advised to undergo corrective surgery. Three patients with stress incontinence had a Marshall Marchetti type of procedure which was followed by relief in 2 cases. Of the 3 patients with constant leakage one underwent urethral advancement (resulting in partial relief), and in 2 who had combined urethral advancement and Marshall Marchetti procedures the constant leakage was converted into tolerable stress incontinence.

Study of Possible Causative Factors

A detailed study of factors which could have contributed towards the occurrence of incontinence was made.

1. Presence of Pre-operative Incontinence. In this series of 238 procedures pre-operative incontinence was recorded in 48 (20%). The incidence of initial post-operative incontinence was significantly higher in the group with pre-operative incontinence ($P<0.01$), but the incidence of persistent incontinence in the 2 groups was not significantly different ($P>0.05$) (Table 2).

2. Incidence of Incontinence Related to Single or Repeat Surgery. Post-operative incontinence after the first procedure occurred in 41 (19.4%), whilst the incidence after repeat procedures was 14.8% (4 out of 27 procedures). These differences were not significant ($P>0.05$).

3. Incontinence in Relation to Main Indications for Surgery. Incontinence was more frequent in patients with bladder neck hypertrophy (22.6%) than in those with bladder neck polypi (7.4%) or neurogenic bladder (16.6%). Statistical analysis showed the differences to be significant between patients with polypi of the bladder neck and bladder neck hypertrophy ($P<0.05$) (Table 4).

Further studies to determine whether any particular type of incontinence was associated with any particular indication for surgery did not reveal a significant correlation ($P>0.05$) (Table 5).

4. Incontinence in Relation to the Type of Procedure. An attempt was made to ascertain whether a modification of the standard procedure of transurethral resection had any effect on the occurrence of post-operative incontinence (Table 6). The incidence of incontinence in the various procedure groups (1 to 6) was 23%, 16.6%, 100%, 16.6%, 7.9% and 15.6% respectively. Statistical analysis revealed the differences to be significant only between groups 1 and 5 ($P<0.05$).

The question of whether any particular type of

Table 6 Occurrence of Incontinence in Relation to Type of Operation

Type of operation	*Incontinence*		*Total*
	Absent	*Present*	
1. TUR bladder neck only	106	31	137
2. TUR bladder neck plus incision of trigone	15	3	18
3. TUI bladder neck only	0	1	1
4. TUR bladder neck polypi only	10	2	12
5. 1 and 4	35	3	38
6. TUR bladder neck and other miscellaneous operations	27	5	32
Total	193	45	238

Table 7 Correlation Between Type of Post-operative Incontinence and Type of Surgery

Type of incontinence	*Type of surgery**					*Total*
	1	*2*	*3*	*4*	*5*	
Urgency	2	0	0		0	2
Stress	17	0	1	1	3	22
Urgency + stress	2	0	0	0	0	2
Constant leakage	6	2	0	1	1	10
Type not recorded	7	1	0	0	1	9
Total	34	3	1	2	5	45

* Type of surgery:
1. TUR bladder neck only.
2. TUR bladder neck plus incision of trigone.
3. TUI bladder neck only.
4. TUR bladder neck polypi only.
5. TUR bladder neck plus other operations.

Table 8 Incidence of Post-operative Incontinence in Relation to Amount of Tissue Removed

Amount of tissue removed	*Post-operative incontinence*		*Total*
	Absent	*Present*	
1 g or less	142	31	173
>1 g	46	12	58
	188	43	231
<5 g	180	44	224
5 g or more	6	1	7
	186	45	231

Table 9 Post-operative Course of Incontinence in Relation to Amount of Tissue Removed

Amount of tissue removed	*Course of incontinence*		*Total*
	Transient	*Persistent*	
1 g or less	23	8	31
>1 g	7	5	12
	30	13	43
<5 g	31	13	44
5 g or more	1	0	1
	32	13	45

incontinence was more likely to occur in association with a particular modification of the procedure was also studied (Table 7). The differences between the various groups were not significant ($P>0.05$).

5. *Incontinence in Relation to the Amount of Tissue Removed at Surgery.* The amount of tissue removed was correlated with the incidence (Table 8), course (Table 9) and type (Table 10) of post-operative incontinence. Comparisons were made between groups with 1 g or less *vis-à-vis* more than 1 g, and those with less than 5 g *vis-à-vis* those with 5 g or more. The amount of tissue removed bore no relationship to the incidence, type and course of post-operative incontinence since the differences between the various groups were not significant ($P>0.05$).

6. *Relationship Between the Existence of Pre-operative Cystocele and the Occurrence of Post-operative Incontinence.* This information was available in 233 instances and the presence of cystocele was recorded in 21.8% (Table 11). The incidence of post-operative incontinence was 35% in those with a cystocele as against 13.8% in those without it. The differences between the 2 groups were highly significant ($P<0.001$). The type of post-operative incontinence (Table 12) bore no significant relationship to the presence or absence of cystocele ($P>0.05$). The presence of a pre-operative cystocele had no influence on whether the incontinence was to be transient or persistent ($P>0.05$) (Table 11).

Table 10 Type of Incontinence in Relation to Amount of Tissue Removed

Amount of tissue removed	*Type of incontinence*		*Total*
	Constant leak	*Others*	
1 g or less	6	16	22
>1 g	4	7	11
<5 g	10	15	25
5 g or more	0	1	1

7. *Occurrence of Post-operative Incontinence in Relation to the Existence of Pre-operative Urethrocele.* The data on this point were available in 221 instances only (Table 11). A pre-operative urethrocele was present in 10%. The incidence of post-operative incontinence was 49% and 16.6% respectively in the groups with and without pre-operative urethrocele. The differences between the groups were highly significant ($P<0.01$). However, the differences between the groups in regard to the type of incontinence (Table 12) or whether it was likely to be transient or persistent (Table 11) were not significant ($P>0.05$).

Discussion

In this study the incidence of post-operative incontinence noted immediately after removal of the catheter was 15.2%, which is substantially higher than that quoted in the literature (Thompson, 1939; Emmett *et al.*, 1950; Nelson *et al.*, 1957). However, a spontaneous and complete cure was noted in about 70% of patients over the following few months, possibly due to control of infection, recovery of detrusor tone and regression of oedema at the vesical outlet. Similar spontaneous remissions have been recorded by others (Kerr *et al.*, 1966; Bonin, 1969). Furthermore, if patients who were incontinent before surgery were to be excluded, the persistent incontinence rate would be 4.7%.

Morbidity from incontinence following alternative procedures is not inconsiderable. The incidence of initial post-operative incontinence after Y-V plasty of the bladder neck in unselected cases was quoted at 37% by Bonin (1969). Although his series was small and the follow-up short, spontaneous remissions were recorded after that procedure also. After "Otis urethrotomy" Kerr *et al.* (1966) reported an initial incontinence rate of 2.6% and a persistent incontinence rate of 1%, and Bonin (1969) reported initial and persistent incontinence rates of 6 and 3% respectively. Ray (1967) reported an incontinence rate of 2% after TUI. In the current series the only patient who underwent transurethral incision developed incontinence afterwards. Keitzer and Allen (1970) reported an incontinence rate of 0.75% even in carefully selected patients undergoing an "Otis

Table 11 Presence of Pre-operative Cystocele/Urethrocele and the Incidence and Course of Post-operative Incontinence

		Post-operative incontinence			*Total*
		Present		*Absent*	
		Transient	*Persistent*		
Cystocele	Present	14	4	33	51
	Absent	17	9	156	172
	Total	31	13	189	233
Urethrocele	Present	7	2	13	22
	Absent	22	11	166	199
	Total	29	13	179	221

urethrotome TUI". It must be remembered that transurethral incisions with an Otis urethrotome or cautery are usually performed in early or less severe cases, whilst transurethral resections and Y-V plasties are reserved for more severe and intractable cases.

Further follow-up studies on patients with persistent incontinence in the present series revealed that most of these patients could be managed either by conservative or surgical measures. Some patients refused further surgery because their symptoms were not unduly severe.

The present study shows that incontinence occurs no more frequently after repeat surgery than after the first procedure, that the incidence and type of incontinence and the chances of spontaneous relief are unrelated (1) to the amount of tissue removed, (2) to any modification of the standard procedure, and (3) to the indications for surgery, except that transurethral resection of polypi at the bladder neck was associated with a significantly lower incidence of incontinence.

The presence of a cystocele or urethrocele increased the incidence of incontinence. Bonin (1969) recommended that Y-V plasty for the bladder neck should be avoided in cases of "bladder neck obstruction" if a cystocele was present. How cystoceles and urethroceles predispose to the occurrence of incontinence is not clear. Patients with a cystocele commonly have a hypertrophied posterior lip of the bladder neck, which may be an important factor in maintaining continence in patients with a defective pelvic floor. Resection or even incision of this posterior lip could predispose to incontinence.

Since the amounts of tissue removed at operation do not correlate well with the incidence of incontinence it would lead one to suspect that there is a strategic zone at the bladder neck from which the removal of even small amounts of tissue may cause incontinence. This would support the concepts of a "continence zone" (Gleason *et al.*, 1974) and a "compression zone" (Griffiths, 1973) at the bladder outlet and in the adjoining urethra.

Even transurethral incision can lead to incontinence (Kerr *et al.*, 1966; Ray, 1967; Bonin, 1969; Keitzer and Allen, 1970). This raises the possibility of a "critical depth" to which a resection/incision can be carried out without causing incontinence. The significantly lower incidence of

Table 12 Relationship of the Type of Post-operative Incontinence to the Existence of Pre-operative Cystocele/Urethrocele

Type of incontinence	*Cystocele*			*Urethrocele*		
	Present	*Absent*	*Total*	*Present*	*Absent*	*Total*
Urgency	1	2	3	0	2	2
Stress	11	10	21	6	13	19
Urgency + stress	0	2	2	0	2	2
Constant leakage	3	7	10	1	9	10
Total	15	21	36	7	26	33

incontinence after TUR of bladder neck polypi would tend to support this view.

The location of the strategic area and critical depth requires further study. Although data comparing anterior, lateral and posterior incisions and resections are not currently available, the general impression is that anterior incisions made with cautery or by the Otis urethrotome lead to a lower incidence of incontinence. The increased incidence after TUR of the bladder neck in cases with cystocele tends to show that the posterior lip of the bladder neck and the adjoining area may be more important in the mechanism of continence.

Another factor thought critical in maintaining urethral continence is the length of the urethra (Lapides, 1958). Urethras less than 2.5 and 3 cm long have been thought to result in incontinence after TUI (Keitzer and Allen, 1970) and Y-V plasty (Bonin, 1969). Data on this point were not available in this series and therefore a correlation could not be obtained, but it is likely that by excluding urethras smaller than the "critical length" the incidence of incontinence can be further reduced.

It seems that one need not be too wary of morbidity following TUR of the bladder neck in women if one considers the poor response to lesser measures and the similar morbidity following alternative procedures. However, a more precise definition of cases suitable for this procedure may help to reduce further the incontinence rate.

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A Comparative Study of the Human External Sphincter and Periurethral Levator Ani Muscles

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Summary—Specimens from the human male and female external urethral sphincter and the periurethral levator ani muscle have been examined using histochemical and electron microscopic techniques.

In both sexes the external sphincter consists of a single population of type I (slow twitch) fibres with a mean diameter of 17.47±0.7 μm in the absence of muscle spindles. In contrast, the periurethral levator ani possesses muscle spindles and the constituent fibres form a heterogeneous population of type I and type II (fast twitch) fibres, with mean diameters of 45.5±0.8 μm and 59.5±3.4 μm respectively.

These findings indicate that the external urethral sphincter is functionally adapted to maintain tone over prolonged periods and may be of considerable importance in producing active urethral closure during continence. The anatomical location and fibre characteristics of the levator ani muscle suggest that these fibres actively assist in urethral closure, particularly during events which cause elevation of intra-abdominal pressure.

In view of the differences in fibre characteristics between the external urethral sphincter and the levator ani, EMG activity recorded from a single site in the levator ani may not be representative of the functional status either of other levator ani muscle fibres or of the external urethral sphincter.

Although it is generally accepted that urethral resistance is dependent upon the combined effects of both intramural and extramural components, the relative importance of each of these factors remains the subject of considerable controversy. Concerning intramural forces, the passive occlusive effects of elastic tissue have been considered by some workers (Lapides, 1958; Woodburne, 1961; Ruch, 1965) to be of considerable importance. Others have placed particular emphasis upon actively contractile mechanisms including smooth (Kleeman, 1970; Donker *et al.*, 1972; Raz and Caine, 1972) and striated (Tanagho *et al.*, 1969; Vereecken and Verduyn, 1970) muscle. In relation to the latter tissue component, dispute also surrounds the functional significance of intramural urethral and periurethral striated muscle in producing urethral closure. On the basis of studies employing neuromuscular blocking agents, some authors (Lapides *et al.*, 1955; Cass and Hinman, 1968) consider that the role of urethral striated muscle is of relatively minor importance. Using similar experimental techniques, others contend that contraction of this musculature plays a prominent part in actively maintaining continence (Tanagho *et al.*, 1969; Vereecken and Verduyn, 1970).

From a morphological standpoint, circularly arranged striated muscle within the wall of the urethra is usually thought to comprise the external urethral sphincter. However, as noted above, the part played by this muscle and by that of the surrounding periurethral muscle of the pelvic floor in the mechanisms of micturition and continence remains uncertain. This confusion is attributable in part to conflicting anatomical descriptions of the arrangement of striated muscle in relation to the urethra. Some workers state that the external urethral sphincter is in direct continuity with the periurethral striated muscle of the levator ani (Curtis *et al.*, 1939; Langreder, 1956) while others state that the 2 muscles are morphologically distinct (Donker *et al.*, 1976; Gosling and Dixon, 1979).

In view of these uncertainties, the present study

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has employed specific histochemical and electron microscopic techniques in an attempt to clarify the functional significance of striated muscle within, and adjacent to, the wall of the human urethra.

Materials and Methods

Fresh specimens of intramural urethral striated muscle (the external sphincter) were obtained from 9 patients undergoing total cystectomy (5 male and 4 female). In males, samples were obtained from the membranous urethra, while in females specimens were obtained from the middle one-third of the urethral wall. In 3 of these patients samples of the levator ani muscle adjacent to the urethra were also obtained. Further samples of periurethral levator ani were obtained from 4 female patients undergoing surgical repair procedures for urinary incontinence. From each tissue sample a small portion was removed and prepared for electron microscopy; the remainder was processed for light microscopy.

Light Microscopy

Tissue samples were mounted in appropriate planes on cryostat tissue holders and rapidly frozen either in 2 methyl butane (isopentane) or dichlorofluoromethane (arcton 12) cooled in liquid nitrogen. Frozen serial sections 10 to 15 μm in thickness were prepared in a cryostat maintained at –25°C internal temperature and processed either for routine histology (Masson, 1929), myosin ATP'ase (Guth and Samaha, 1970) or tissue succinate dehydrogenase (Nachlas *et al.*, 1957).

Myofibrillar Adenosinetriphosphatase (ATP'ase)

Sections were pre-incubated for 15 min at 20°C either in 18 mM calcium chloride in 100 mM 2-amino-2-methyl-1-propanol at pH 10.4 (for alkali-stable myosin ATP'ase), or in 50 mM potassium acetate in 18 mM calcium chloride at pH 4.35 (for acid-stable myosin ATP'ase). All sections were then incubated at 37°C in solutions containing 2.7 mM ATP, 50 mM potassium chloride and 18 mM $CaCl_2$ in 100 mM 2-amino-2-methyl-l-propanol at pH 9.4 for 5 to 20 min. Following incubation, sections were developed in 1% ammonium sulphide for 3 min, dehydrated in graded alcohol, cleared in xylene and tetrachloroethylene and mounted in Canada balsam.

Tissue Succinate Dehydrogenase

Appropriate tissue sections were incubated at 20°C for 15 to 18 h in a solution containing 10 ml of 0.1 M sodium succinate, 10 ml of formdimethylamide, 10 ml of 0.1 M phosphate buffer at pH 7.6 and 20 mg of Nitro Blue Tetrazolium as substrate. Subsequently the sections were either mounted in glycerine jelly or dehydrated through graded alcohol, cleared in xylene and tetrachloroethylene and mounted in Canada balsam.

Electron Microscopy

From each specimen, portions 1 mm^3 in size were fixed in ice-cold 1% osmium tetroxide in acetate veronal buffer at pH 7.3 for 1 h (Palade, 1952). After fixation the tissue pieces were dehydrated in ascending concentrations of ethyl alcohol and embedded in epoxy resin with the aid of propylene oxide. Thin sections were cut using glass knives and a Reichert 0m U3 ultramicrotome, mounted on uncoated copper grids, double stained with alcoholic uranyl acetate (Watson, 1958) and lead citrate (Reynolds, 1963) and examined in a Philips EM300 electron microscope.

Results

The following account of observations on the external urethral sphincter and on the periurethral levator ani muscle applies to both males and females since, for each muscle, sex differences have not been observed. Furthermore, samples obtained from female patients undergoing surgery for urinary incontinence were similar to those obtained from the other patients included in this study.

Histochemical Fibre Typing

According to the classification of Padykula and Herman (1955), type I (slow twitch) fibres are rich in acid-stable myosin ATP'ase and are correspondingly low in alkaline-stable myosin ATP'ase. In contrast, type II (fast twitch) fibres contain relatively low concentrations of acid-stable myosin ATP'ase, but are rich in alkaline-stable myosin ATP'ase. This system has been employed in the present study to classify the types of fibre which constitute the external urethral sphincter and the periurethral levator ani muscle.

Cryostat sections of external urethral sphincter processed for myosin ATP'ase demonstrated a homogeneous population of small diameter, type

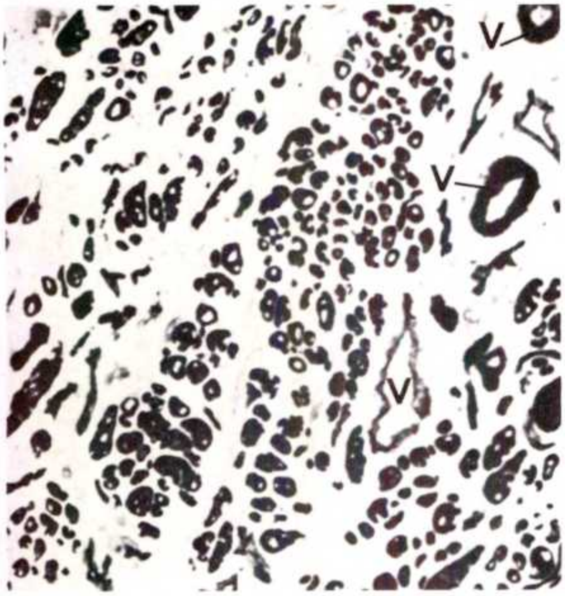

Fig. 1 Photomicrograph of a section of the external urethral sphincter processed for acid stable myosin ATP'ase. All of the striated muscle fibres are darkly-staining (type I) and have relatively small diameters. V, blood vessels (× 150).

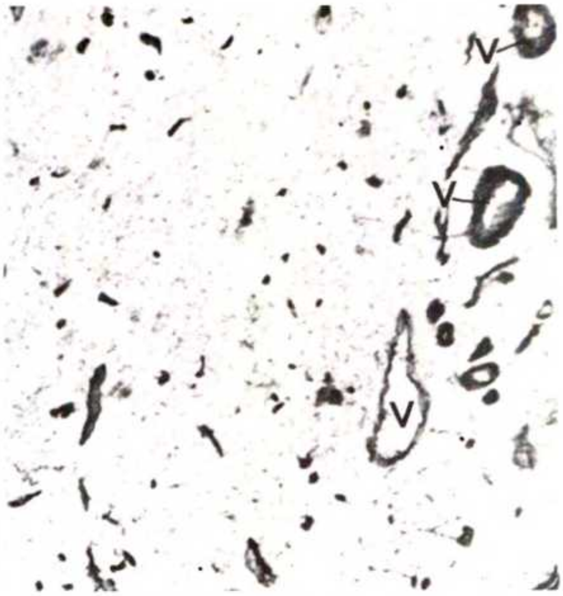

Fig. 2 Photomicrograph of a section adjacent to that shown in Figure 1 processed for alkaline stable myosin ATP'ase. Note the low content of enzyme in the muscle fibres (*i.e.* absence of type II fibres). V, the same vessels as those labelled in Figure 1 (× 150).

I fibres arranged as a circular collar around the urethral lumen. Following acid pre-incubation each muscle fibre was rich in enzyme reaction product (Fig. 1), while on adjacent sections processed using alkaline pre-incubation the same fibres appeared pale-staining (Fig. 2). In contrast, sections of the periurethral levator ani processed for myosin ATP'ase demonstrated an admixture of 2 distinct populations of muscle fibres. Following acid pre-incubation numerous dark-staining (type I) fibres were interspersed with pale-staining (type II) fibres within each muscle fascicle (Fig. 3). On adjacent sections processed using alkaline pre-incubation the reverse staining pattern was obtained (Fig. 4). Using additional adjacent sections processed to demonstrate succinate dehydrogenase, type II fibres possessed a lower content of enzyme than type I fibres.

Careful examination of serial sections of the external sphincter has failed to demonstrate muscle spindles, although these structures have been observed in samples from the periurethral levator ani (Fig. 5).

Quantification of Fibre Diameter

Comparing sections of the external sphincter with those from the levator ani, a marked difference in diameter of the constituent fibres has been noted. In order to quantify these differences, randomly chosen areas from sections of each muscle processed for acid-stable myosin ATP'ase were projected on to paper at constant magnifica-

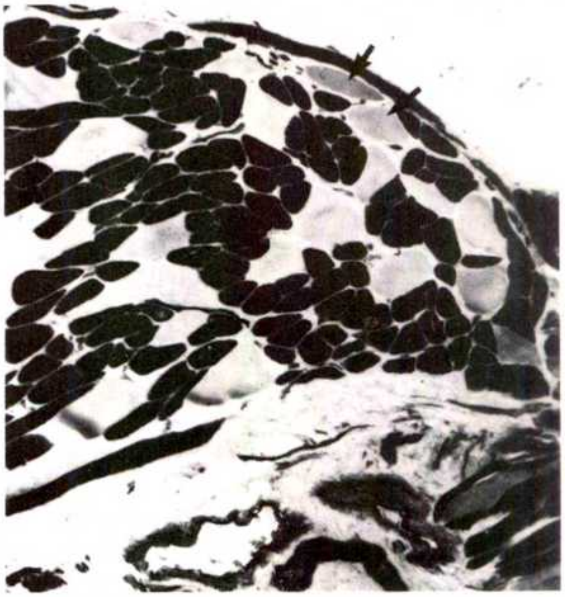

Fig. 3 Photomicrograph of a section of periurethral levator ani processed for acid stable myosin ATP'ase. The predominance of darkly-stained type I fibres is clearly seen amongst the pale-stained type II fibres. Arrows indicate 2 type II fibres (× 150).

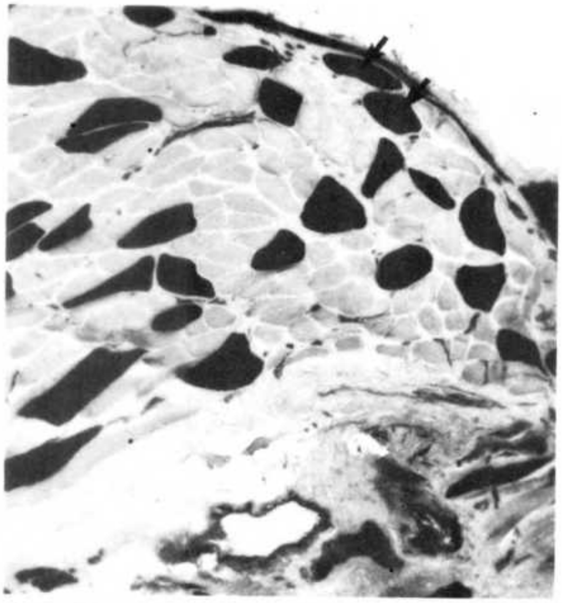

Fig. 4 Photomicrograph of a section adjacent to that shown in Figure 3 processed for alkaline stable myosin ATP'ase. Type I fibres are now pale-stained while type II fibres are rich in enzyme. Note that the same fibres indicated in Figure 3 (arrows) are darkly-stained (× 150).

tion (× 166) and the outlines of individual transversely-sectioned muscle fibres were recorded. The narrow diameter of each fibre outline was then measured and a mean value calculated for the component fibres of both the external sphincter and the levator ani muscle. From specimens of the former the value obtained for the mean diameter of type I fibres was $17.47 \pm 0.7 \mu m$ (standard error of the mean). In contrast, the values obtained for the mean diameters of type I and type II fibres from the levator ani were 45.5 ± 0.8 μm and 59.5 ± 3.4 μm respectively. In addition, the numbers of type I and type II fibres within each sample area of the levator ani were counted in order to determine their relative proportions. On average it was found that type II fibres constituted 5% of the population, while 95% of fibres were type I.

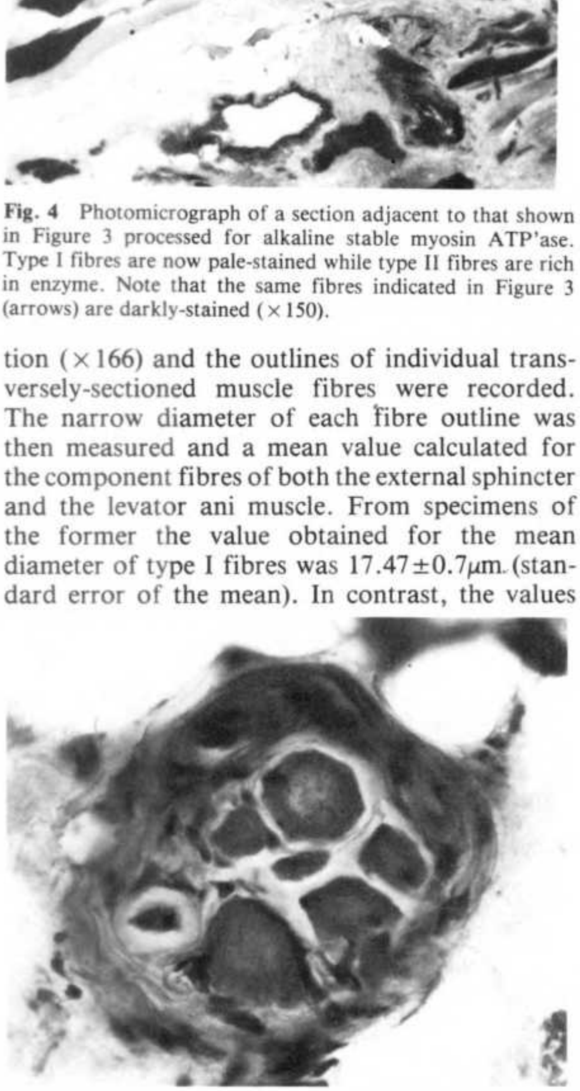

Fig. 5 Photomicrograph of an encapsulated muscle spindle from a section of periurethral levator ani (Masson's trichrome stain × 300).

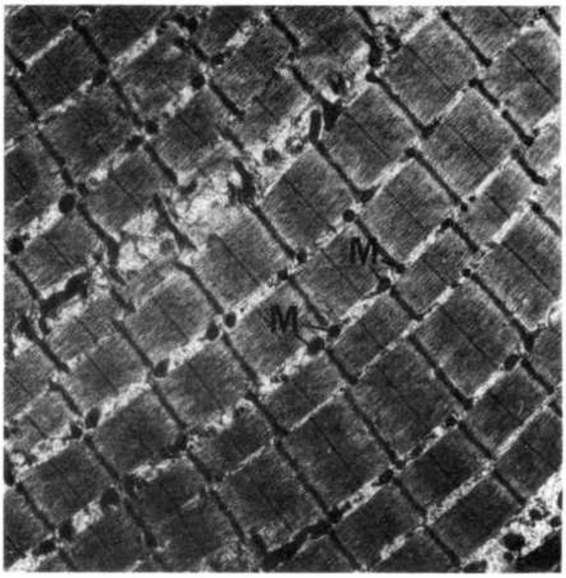

Fig. 6 Electron micrograph of a type I muscle fibre from the periurethral levator ani. Note the rows of paired mitochondria (M) between adjacent myofibrils (× 10,000).

Electron Microscopy

It is now generally accepted that type I striated muscle fibres may be distinguished from type II fibres using electron microscopy (Padykula and Gauthier, 1967). Using this classification, type I fibres possess numerous mitochondria (many of which aggregate beneath the sarcolemma), are associated with a relatively high content of lipid droplets, and possess wide Z discs.

In the present study these criteria have enabled 2 fibre types to be morphologically distinguished in specimens of the levator ani muscle. The majority of fibres were identified as type I, being richly endowed with mitochondria arranged in rows between the myofibrils (Fig. 6). Clusters of large, polymorphic mitochondria were also observed adjacent to the sarcolemma, particularly in the perinuclear zones. In general, the mitochondria-rich striated muscle fibres also contained numerous pale-staining lipid droplets. However, the amount of lipid varied considerably not only between the individual specimens of levator ani, but also from one fibre to another. The majority of such lipid droplets were spherical in outline and were frequently observed in close association with mitochondria. A very small proportion of fibres of the levator ani muscle were identified as type II on the basis of their relative paucity of mitochondria and lipid (Fig. 7). In general, the mitochondria of type II fibres were smaller than those of type I, appeared oval in cross-section rather than polymorphic, and failed to form aggregations in the subsarcolemmal zones. In the present study no attempt has been made to measure Z disc width in either fibre type.

Concerning sections obtained from the samples of external sphincter, all of the muscle fibres appeared similar in fine structure and were identified as type I, being rich in polymorphic mitochondria (Fig. 8). Fibres corresponding morphologically to type II were not observed in any specimen of external urethral sphincter.

Discussion

The present study has shown that while the results obtained using male and female specimens are similar, significant morphological differences exist in both sexes when the constituent fibres of the external urethral sphincter are compared with those of the periurethral levator ani. Using routine histological techniques, previous workers (Von Hayek, 1960) have noted that the external urethral sphincter is composed of muscle fibres which have approximately one-third the diameter of those forming the levator ani. Similar qualitative observations have been made in the present study and have been confirmed using quantitative techniques. In addition, the present results have shown that the fibres of the external urethral sphincter are rich in acid-stable myosin ATP'ase—an enzyme contained by muscle fibres functionally classified as slow twitch (type I). That these fibres correspond to those of the slow twitch type has been endorsed by the demonstration of their high content of the mitochondrial enzyme succinic dehydrogenase. Furthermore, electron microscopy has confirmed the high mitochondrial content of these intramural urethral striated muscle fibres.

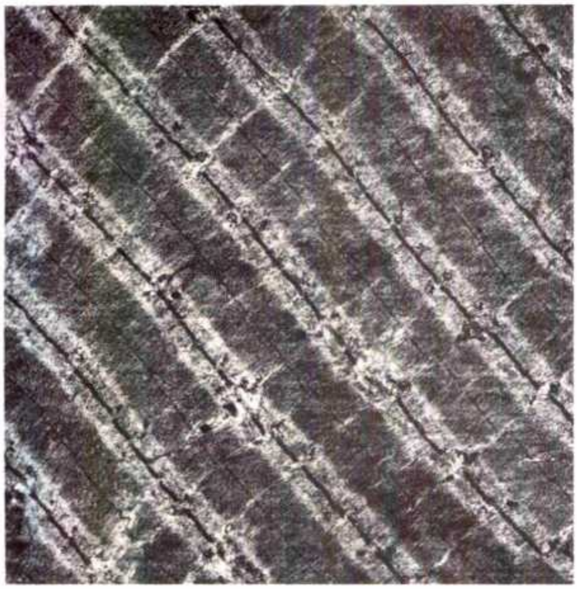

Fig. 7 Electron micrograph of a type II muscle fibre from the periurethral levator ani. By comparison with Figure 6 the relative paucity of mitochondria is clearly evident (× 12,500).

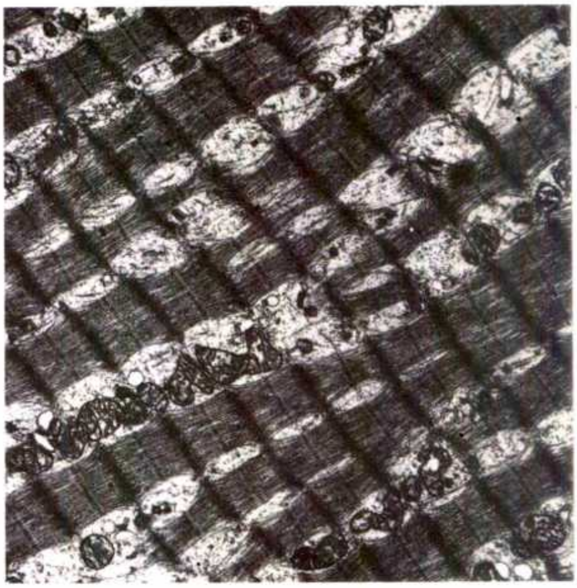

Fig. 8 Electron micrograph of a type I striated muscle fibre from the external urethral sphincter containing numerous mitochondria (compare with Fig. 6) (× 11,200).

Collectively, these observations provide evidence that the striated muscle of the external urethral sphincter consists of specialised fibres which are functionally capable of maintaining tone over prolonged time periods without fatigue. The circular orientation of these fibres is clearly compatible with a sphincteric action and the results emphasise the particular importance of intramural striated muscle in producing urethral closure and thereby actively participating in the maintenance of urinary continence.

Other significant morphological differences are apparent when the external urethral sphincter and the periurethral levator ani muscles are compared. For example, muscle spindles were not observed in any of the specimens of the urethral wall, despite careful study of serial sections. Such structures were frequently observed in the samples of periurethral levator ani. Thus, whilst the latter possesses receptors which are known to modulate the activity of voluntary muscle, the peripheral control of the external urethral sphincter apparently depends upon some other, as yet unknown, mechanism. However, in the absence of such a peripheral mechanism, the tonus of the external urethral sphincter may be controlled entirely by the central nervous system. Whatever the precise mechanism, the absence of muscle spindles further emphasises the differences which exist between typical voluntary muscle and that which constitutes the external urethral sphincter. In this context it is interesting to speculate upon the relatively minor fall in resting urethral pressures which follows the administration of neuromuscular blocking agents (Dortermann and Bauer, 1955; Donker *et al.*, 1972; Bowen *et al.*, 1976). Rather than interpret this response as an indication of the minor role played by the external urethral sphincter in generating urethral resistance, it may well be that this specialised striated muscle is relatively insensitive to the effects of neuromuscular blocking agents such as curare.

Concerning the periurethral striated muscle, the constituent fibres in both sexes are separated by a continuous connective tissue septum from the external urethral sphincter (Donker *et al.*, 1976; Gosling and Dixon, 1979). In addition, the present histochemical techniques have shown these muscle cells to consist of a heterogeneous population of large diameter type I and type II fibres. Using quantitative methods the proportion of type I fibres is greater than type II, confirming that the majority of periurethral striated muscle fibres are also functionally of the slow twitch type. That the periurethral levator ani is composed of muscle fibres in these relative proportions is of considerable interest and may be related to the role played by this muscle in actively supporting the pelvic viscera. It is well known that motor unit activity can be recorded from periurethral muscle using EMG techniques with the subject "at rest" and it seems likely that slow twitch type I fibres similar to those demonstrated in the present study are responsible for this background activity.

Unlike the external urethral sphincter, the levator ani also contains a population of fast twitch (type II) fibres functionally associated with rapid, forceful muscle contraction. These fibres are probably recruited to increase the force and speed of contraction of the levator ani during those events which raise intra-abdominal pressure (such as coughing, sneezing, etc.).

In general, the present findings endorse the view that periurethral striated muscle assists the external urethral sphincter in active urethral closure not only to ensure continence but also to produce rapid, forceful occlusion of the urethra such as occurs during voluntary interruption of micturition.

Finally, the morphological differences which exist between the component fibres of the external urethral sphincter and periurethral striated muscle must be borne in mind when the results of EMG studies applied to those regions are interpreted. Clearly the activity recorded from a single site in the levator ani may not be representative of the functional status of other levator ani muscle fibres or of the external urethral sphincter.

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Penile Injuries with Particular Reference to Injury to the Erectile Tissue

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Summary—A retrospective study of 56 patients with penile injuries showed that 28 injuries were sustained during coitus and a further 12 in other sexual practices. Four different types of injury to the erectile mechanism are described and the management of each discussed.

A modified phalloplasty technique is described for patients who have sustained a complete loss of the phallus.

Penile injuries are uncommon and accounted for only 5% of the urological injuries sustained in Vietnam (Selikowitz, 1977). The pattern of injuries seen in civilian practice is different and this paper concentrates on those injuries which are associated with sexual difficulties and excludes acute injuries of the urethra.

Patients

The records of 56 patients seen during the past 5 years with penile injuries were reviewed and the injuries classified. This was performed on an anatomical basis according to the main functional site of the injury (Table 1). Complex injuries are those where there was loss of skin, erectile and urethral tissues.

The mechanism of injury is shown in Table 2, where it can be seen that 50% of the injuries occurred during coitus and a further 21% occurred as a result of other sexual practices. Four iatrogenic injuries followed the faulty use of the urinary incontinence apparatus and 3 as a complication of circumcision. There were no diathermy injuries of the penis in this series.

Results

The salient features of each group of injuries are described but emphasis has been placed upon those injuries where there was damage to the erectile tissue.

Table 1 Classification of Penile Injuries

Skin	21
Erectile	24
Urethral	4
Complex	7
Total	56

Skin Injuries

Twenty-one patients with a skin injury (Table 3) were managed along conventional lines to ensure rapid healing of the wound. Prophylactic antibiotics were used to prevent the occurrence of Fournier's gangrene and temporary urethral catheterisation was carried out in those patients with extensive wounds. Skin grafting was necessary for one of the patients who had sustained a degloving vacuum cleaner injury.

The 12 patients with a torn frenulum presented with pain, bleeding and penile ulceration following coitus. Spontaneous resolution of the symptoms occurred in 3 patients but satisfactory post-operative results were obtained in the remainder, following circumcision in one patient, "Z" plasty in 2 patients and simple frenuloplasty, when the transverse division of the frenulum was sutured longitudinally, in 6 patients.

Table 2 Mechanism of Injury

	Skin	*Erectile*	*Urethral*	*Complex*
Accidental	3	6	—	1
Coital	12	16	—	—
Self inflicted	4	—	2	2
Second party	—	2	—	1
Iatrogenic	2	—	2	3

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 3 Injuries to Penile Skin (21 Patients)

Number of patients	*Aetiology*	*Age (years)*
12	Torn frenulum	29 (mean)
1	Zipper	12
2	Burns	25, 33
2	Tight incontinence device	27, 48
3	Vacuum cleaner	55, 60, 66
1	Metal nut strangulation	58

Urethral Injuries

Acute urethral injuries have been excluded from this paper and the 4 patients included all presented with a urethral fistula following penile injury. Two fistulae occurred following childhood circumcision and in one 10-year-old boy as a result of hair strangulation. In the fourth patient, a 27-year-old man, the fistula occurred following the application of hydrogen peroxide to a "septic spot". In each instance the fistula was closed in layers with rotation of a skin flap.

Erectile Tissue Injuries

Eighteen of the 24 injuries occurred during various sexual practices but only 4 of the patients were seen by a doctor within 24 h of their injury. Eighteen patients were referred for treatment of "Peyronie's disease" but trauma appeared to be an aetiological factor in only 8% of the 222 patients with this condition seen by one of the authors (J.P.P.). Injuries of the erectile mechanism may be classified into 4 groups (Table 4) and it is apparent that the classical "faux pas de coit" covers a variety of injuries.

(1) Suspensory Ligament Injuries—2 Patients

This injury may be sustained when the erect penis is forcibly displaced towards the feet. It is painful and may be accompanied by a snapping sensation and bruising sometimes occurs. The patient subsequently recovers some erectile capacity, although there may be some secondary impotence. On erection the penis does not assume the usual position and on clinical examination it is possible to detect an abnormal gap between the symphysis pubis and the penile shaft. There is no palpable swelling once the bruising has subsided. Inflation of the penis with saline or a contrast medium may be used to confirm the abnormality of a "flail" penis.

Table 4 Injuries of Erectile Mechanism

Nature of injury	*Number of patients*
Ruptured suspensory ligament	2
Ruptured tunica albuginea	10
Traumatic cavernous fibrosis	12
Dislocation of the penis	0

This injury occurred to 2 men in the present series. The first, aged 25 years, was managed successfully by anchoring the penis to the symphysis pubis (Pryor and Hill, 1979), whilst no surgical treatment was necessary for the second patient. He presented with secondary impotence which had occurred after a similar injury to that sustained by the first patient. Penile tumescence returned following the accident but the erection was abnormal and coitus impossible. He developed secondary impotence and was referred for evaluation 18 months after the accident. With reassurance and the demonstration to the patient of a normal erection by cavernosography, normal potency was regained and the exact nature of the injury must be open to doubt.

(2) Rupture of the Tunica Albuginea—10 Patients

The classical mechanism of this injury is for the penis to be forcibly bent double during coitus. This may occur by simple misfortune or as a result of sexual athleticism. The injury causes a searing pain and may be accompanied by a sound and detumescence. "Cracked like a whip" was the description used by one patient and the sound was also heard by his wife and this was not an uncommon occurrence. Four patients were seen within 24 h of the injury and the penis was usually swollen and became bruised. Two patients noticed profuse urethral bleeding—a sign of rupture into the urethra, and one of these required catheterisation for urinary retention. The catheter was removed 9 days after the injury and urethroscopy showed a 0.75 cm defect in the urethra about 3 cm from the external meatus. This healed satisfactorily without any complications.

Two of the 4 patients seen acutely were inebriated at the time of the "faux pas de coit". The typical history of a fractured penis during coitus was obtained from 5 additional patients with the typical findings of Peyronie's disease. The final patient was awoken by a "sharp cracking noise" in the penis which was also heard by his wife and it is possible that the penis was injured during a period of nocturnal tumescence.

Two of the 3 acute injuries resolved completely with no lasting disability and one patient was lost to follow-up. The fourth patient developed an atypical Peyronie's disease with a hard plaque of fibrous tissue between the corpora cavernosa and the corpus spongiosum in the mid-shaft of the penis. Resolution of the disability occurred in only one of the 6 patients who presented with Peyronie's disease due to rupture of the tunica albuginea. One patient has had the erectile deformity corrected by the Nesbit operation (Pryor and Fitzpatrick, 1979) and the remainder are still under evaluation and awaiting operation.

(3) Traumatic Cavernositis or Cavernous Fibrosis —12 Patients Twelve patients are classified in this category but there may be some overlap between this and the preceding group: 6 patients sustained a faux pas de coit when the penis was flexed during coitus. The accident was not as painful as in the previous group and was not accompanied by a sound or bruising. Detumescence was not inevitable but the pain sometimes persisted for a week. The patients subsequently noticed a lump in the penis, the presence of an erectile deformity and some impairment of erection. One patient in this group was seen soon after the injury and was noted to have a brawny induration of the penis. Steroids did not improve the induration but the condition slowly resolved over the subsequent 18 months.

In 3 patients the penis was injured during other sexual practices and in the remaining patients the nature of the injury is open to doubt. That injury to the flaccid penis can cause erectile tissue damage is illustrated by the patient who slipped whilst vaulting a fence. He injured the base of his penis, developed a lump and marked impairment of erection. There were no urinary symptoms and he has a normal urethrogram. A cavernosogram (Fig. 1) shows an area of non-filling in the left corpus cavernosum and the penis lacked sufficient rigidity for penetration. The condition failed to resolve and resection of the corpora cavernosa and re-anastomosis did not lead to an improvement. Histology of the resected segment showed that fibrosis of the erectile tissue had occurred (Fig. 2). He has subsequently received a penile implant and is well satisfied with the result, although Abrahamy and Leiter (1980) have described a similar case which was cured by anastomosing the corpora cavernosa together.

The natural history of his cavernous fibrosis is unknown but spontaneous resolution has been seen in the one patient who was seen soon after injury. The remaining patients were managed in the same manner as other patients with Peyronie's disease.

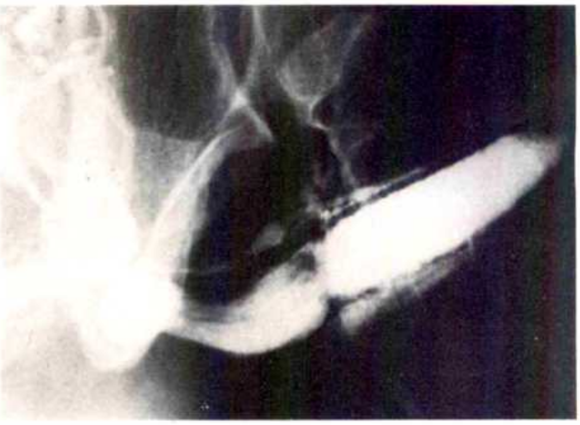

Fig. 1 Cavernosogram of patient with traumatic cavernous fibrosis showing an area of underperfusion.

(4) Dislocation of the Penis This is an even less common injury and was not encountered in the present series of patients. Early reduction is necessary and delayed complications are unusual (Shiraki and Trichel, 1969).

Complex Injuries

Two elderly men developed gangrene of the glans penis following the faulty use of a condom drainage apparatus in a 67-year-old paraplegic or of a penile clamp in a 69-year-old man. These patients were treated with catheterisation and antibiotics. The gangrenous areas were excised after demarcation and subsequently healed satisfactorily, although with loss of penile length.

The total loss of phallus was seen in 5 young adults (Table 5). One man amputated his penis whilst depressed and another accidentally chopped off his penis whilst cutting wood. The penis was resutured to the body and when the patient was seen 7 years later the penis looked normal, as did the urethrogram. The patient has subsequently been seen by numerous psychiatrists—all of whom say that he is of normal mentality—but he required penile amputation for pain.

Two of the patients have undergone phalloplasty using a modification of the technique described by Peters (1976). In that operation a tubed abdominal pedicle graft is prepared and a free skin graft used to construct the neo-urethra. In the modified technique (Fig. 3) the neo-urethra is formed from epilated scrotal skin.

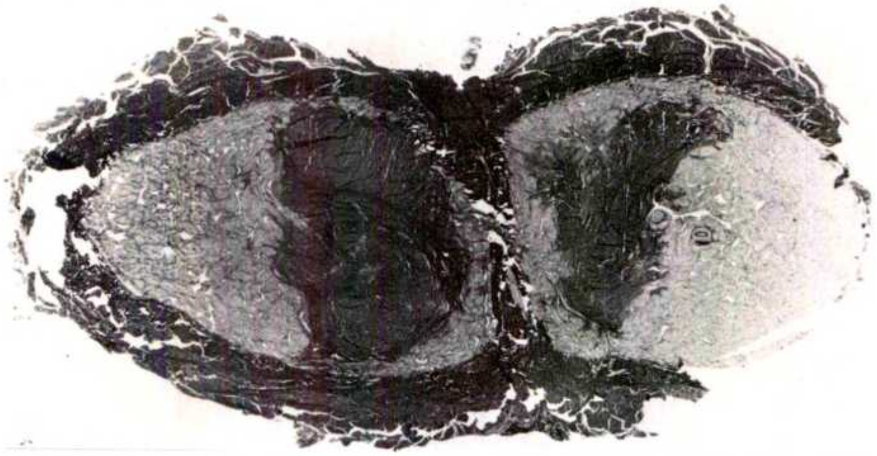

Fig. 2 Whole section mount of the patient with traumatic cavernous fibrosis showing fibrous tissue within the erectile tissue and separate from the tunica albuginea (Van Gieson's stain).

Discussion

The management of skin and urethral injuries requires little comment. The torn frenulum is a nuisance to the patient rather than a serious problem and we feel that circumcision is unnecessary and should be carried out only when there is an element of phimosis.

Masturbation injuries to the penis are usually encountered in older men. The vacuum cleaner injury was described by Fox and Barrett in 1960 and there have been periodic descriptions of strangulation by foreign bodies (Punekar *et al.*, 1978) and hair (Thomas *et al.*, 1977; Singh *et al.*, 1978). The latter injury usually occurs in boys and it is suspected that the injury may be a form of child abuse. Similarities between hair strangulation of the penis, which may result in complete transection of the penile shaft, and Koro disease in the Far East should be noted.

The proposed classification of injuries to the erectile mechanism of the penis is a useful aid to management. The diagnosis of the suspensory ligament injury is based upon the history, palpation of the defect between the symphysis pubis and the penile shaft when it is held vertically, and upon confirmation by giving the patient an artificial erection. This is best achieved using a size 19 scalp-vein needle inserted into the corpora cavernosa and by infusing saline with the aid of a pressure infusor (Fenwall bag).

The distinction between the rupture of the tunica albuginea (fractured penis) and traumatic cavernous fibrosis is made on the history and physical findings. A fracture of the penis usually occurs to the erect organ and since the papers of Meares

Table 5 Total Amputation of Penis Following Trauma

Age (years)	*Mechanism*	*Management*
1.5	Circumcision, infection→amputation	Phalloplasty aged 25
21	Auto-amputation, depression	Stump sutured
26	High velocity missile	Phalloplasty
29	Accidental (chopping wood!)	Primary reanastomosis Excellent function Secondary amputation for pain
35	Unexplained: homosexual	Stump sutured

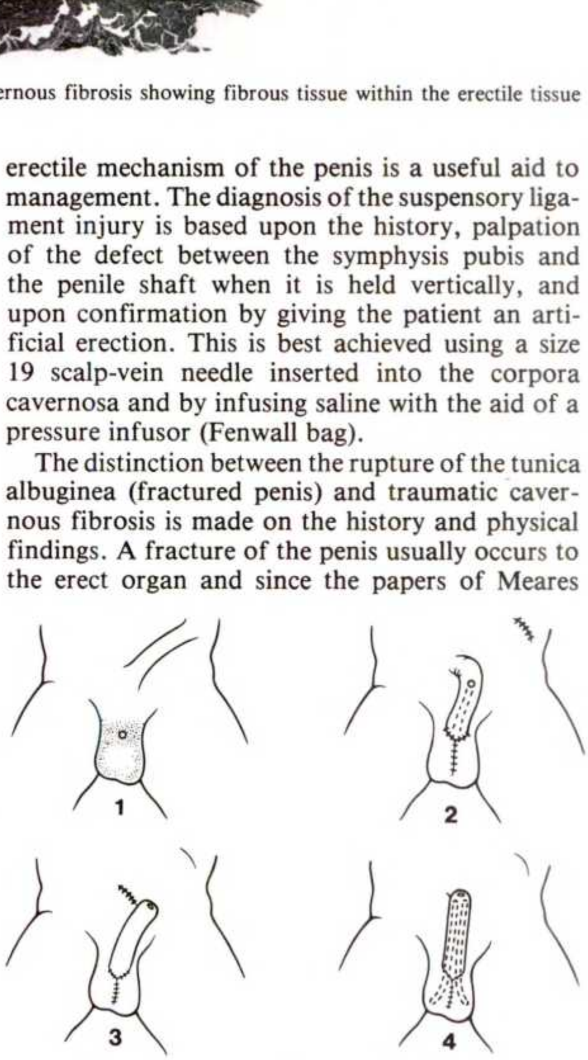

Fig. 3 Technique for phalloplasty following total amputation of phallus. 1. Epilation and formation of pedicle skin flap. 2. Rotation of pedicle graft and formation of neo-urethra with scrotal skin. 3. Detachment of graft. 4. Insertion of silastic penile implant(s).

(1971) and Gross *et al.* (1971) there has been a tendency towards surgical management. This had previously been described by McCrea in 1940. Spontaneous healing occurs in many patients without the necessity for surgical intervention and we would suggest that operation is only necessary when there is a large haematoma which requires evacuation. Chromic or Dexon sutures may then be placed in the tunica albuginea to repair the rent. The recent reports by Walton (1979) and Jallu *et al.* (1980) also describe the favourable results of conservative management.

Complete recovery of function does not occur in all patients with a fractured penis, irrespective of their treatment, and when fibrosis occurs a peripheral plaque of fibrous tissue may be palpated in the position of the tunica albuginea. Such a patient has the typical symptoms of Peyronie's disease and the persistence of such a deformity is best treated by the Nesbit procedure.

The fractured penis may be accompanied by damage to the underlying erectile tissue with a variable degree of fibrosis. A direct blow or a "faux pas de coit" may damage the erectile tissue without rupturing the tunica albuginea. This injury may be described as traumatic cavernous fibrosis and the typical presentation and course differ from those of the fractured penis. The initial pain is less severe but the subequent loss of erectile capacity is greater. On palpation of the penis the mass is found to be more centrally placed than in the typical findings of Peyronie's disease. Spontaneous resolution may occur but a persistent deformity is treated as for Peyronie's disease.

Immediate re-suturing of the amputated phallus is always worthwhile (Bux *et al.*, 1978) and a microvascular technique is not essential. Some patients with traumatic loss of the penis will require subsequent phalloplasty. Complications are common following all types of this operation and occur mainly from the neo-urethra. The use of the epilated scrotal skin to create the new urethra appears to be a good method for ensuring a well vascularised phallus.

Penile injuries are uncommon and treatment should aim at restoring function rather than anatomical structure. Patients with an injury to erectile mechanism often fail to seek medical advice with the acute injury. This retrospective study has emphasised the diverse origin and pathology of penile injuries. Many patients have a permanent disability and it is possible to ameliorate the effects of this by operative treatment.

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The Intravenous Urogram in Acute Epididymo-orchitis

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Summary—In a series of patients presenting with acute epididymo-orchitis, the abnormalities detected on intravenous urography were analysed.

Urography is recommended in patients aged over 50 and in pre-pubertal boys, but it did not prove useful in adult patients under 50 years of age without other symptoms.

It has been the practice in this department to perform intravenous urography within 6 weeks of presentation in all cases of epididymo-orchitis to exclude underlying urinary tract abnormalities which might have contributed to the development of the disease. A retrospective review was undertaken to determine the frequency of such abnormalities.

Patients and Methods

Studies were carried out on 130 consecutive patients presenting between 1957 and December 1978 with a diagnosis of acute epididymo-orchitis made either on physical examination or, in cases of doubt, by exploration of the scrotum. Cases of relapsing and chronic epididymo-orchitis were excluded if details of the initial episode were not available. Patients who presented with acute disease, however, and who subsequently demonstrated chronicity, were included in the series. Mumps orchitis was also excluded.

All patients had intravenous urography to detect underlying abnormalities. Particular note was taken of the following from the case histories: (1) the presence of organisms in a midstream specimen of urine, (2) the existence of predisposing factors in the history, such as trauma, recent urological operations and heavy lifting, (3) the presence of pre-existing urological symptoms at the time of presentation.

Patients were divided into 3 age groups: pre-pubertal boys, adults between puberty and 50 years, and adults over 50 years.

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Results

The age distribution of patients and the overall incidence of abnormalities on intravenous urography, whether or not of clinical importance, are shown in Table 1.

All 3 boys in the pre-pubertal group underwent surgical exploration as an emergency to exclude torsion of either the testis or an appendage and at operation a diagnosis of acute epididymo-orchitis was made. All had normal urograms and subsequent urine examination failed to demonstrate infecting organisms or pus cells in significant quantities. One of these boys, a 10-year-old, had epididymo-orchitis in an ectopic testis lying in the superficial inguinal pouch. Exploration established the diagnosis and a dartos pouch orchiopexy was performed.

Six of the 68 patients in the puberty to 50-year age group had abnormalities on intravenous urography (Table 2). A duplex right kidney without pus in the urine was found in one of these cases. One patient with clubbing of the upper and middle calices of the left kidney, consistent with tuberculous infection, had a sterile pyuria and *Mycobacterium tuberculosis* was subsequently cultured from the urine. It is uncertain whether his scrotal inflammation was a result of the tuberculous infection, since the absence of organisms from

Table 1 Age Distribution of Urographic Abnormalities

Age group	*No. of patients*	*No. of patients with abnormal urogram*
Pre-pubertal	3	0
Puberty to 50 years	68	6 (9%)
Over 50 years	59	25 (42%)
Total	130	31 (24%)

Table 2 Abnormalities in the Puberty to 50-year Age Group

Age	*Abnormality on urography*
21	Small, poorly-functioning right kidney. Right ureterocele: normal function on left
25*	Left-sided bladder diverticulum with bladder neck obstruction
26*	Left-sided bladder diverticulum with residual urine. Bladder neck obstruction with bilateral vesicoureteric reflux
28	Clubbing of the left upper and middle calices suggestive of tuberculosis
29	Duplex right ureter
48	Moderate residual urine with basal prostatic filling defect

* Denotes patients with urinary symptoms.

the urine does not exclude coincidental acute, non-specific epididymo-orchitis. Two patients had urinary symptoms of bladder neck obstruction and the urogram showed residual urine with bladder diverticula. They subsequently underwent operative procedures upon the bladder neck, resulting in relief of symptoms. One patient had no symptoms of outflow obstruction but some residual urine which was probably of little significance. The sixth patient, a 21-year-old, had a small, poorly-functioning right kidney above a right ureterocele. Since he was asymptomatic, failure to perform a urogram would have missed this. He was the only patient in whom a serious abnormality would have been missed and represents less than 2% of the 68 patients.

An analysis of the urograms in 59 patients over the age of 50 showed that in 25 (42%) there were abnormalities (Table 3). Seventeen of these patients were found to have residual urine and 2 had bladder diverticula. They all had a history suggestive of bladder outflow obstruction sufficient to warrant a urogram. Eight of these patients were shown to have significant pathogenic bacteria in the urine. There were 2 incidental findings of a simple renal cyst and a multicystic kidney, and both of these patients had sterile urine. The remaining 6 patients (9%) had a significant abnormality with no symptoms and these findings would have been missed if a urogram had not been performed. All 6 had infected urine.

Table 3 Abnormalities in Patients Over 50 Years

No. of patients	*Abnormality on urography*
1	Left hydroureter and hydronephrosis. No function on right following prostatectomy
1	Multicystic left kidney
1	Small, poorly-functioning right kidney with vesicoureteric reflux: normal on left
1	Right simple renal cyst
2	Bilateral chronic pyelonephritis secondary to vesicoureteric reflux
2*	Moderate residual urine with bladder diverticulum
2	Left renal calculus
15*	Moderate residual urine with basal prostatic filling defect
25	Total

* Denotes patients with urinary symptoms.

Combining all age groups, 31 urographic abnormalities were detected, of which 28 were considered to be contributory to the disease process. Twenty-five of these 28 were in the over 50-year age group.

Discussion

Acute epididymo-orchitis is a common clinical problem in urological practice, sometimes accounting for up to 24.5% of all urological admissions (Wolin, 1971). In 55 to 100% of cases there is no clear aetiology (Harnisch *et al.*, 1977). It has been postulated that an important factor is reflux of urine from the full bladder into the vas deferens during physical exertion (Badenoch, 1953). However, urethrovasal reflux has seldom been demonstrated in the normal prostatic urethra in the absence of infection. It has been suggested that, in order to produce urethrovasal reflux, one must have either urinary infection or a combination of physical deformity of the verumontanum and deformity of the ejaculatory duct check valve (Kohler, 1962). It has also been suggested that the majority of cases are secondary to prostatitis, seminal vesiculitis or posterior urethritis (Wesson, 1961). Trauma was a precipitating factor in approximately 13.5%, possibly as a result of activation of infection lying dormant in the epididymis (Mittemeyer *et al.*, 1966).

Our results suggest that, in patients with acute epididymo-orchitis and no preceding history of urinary problems, abnormalities are uncommon in patients under 50 years of age. In those aged over 50 years there is a higher incidence of anomalies and not all of these are associated with outflow obstruction.

Acute epididymo-orchitis is rare in pre-pubertal boys and our series of 3 cases was too small to draw any satisfactory conclusions. In children it is difficult to distinguish epididymo-orchitis from torsion of the testis or its appendage, a small incarcerated inguinal hernia or idiopathic scrotal oedema; hence exploration is usually necessary. Although Haahr and Sparrevohn (1971) found no serious abnormalities in 6 cases of epididymo-orchitis, we believe that they are correct in recommending intravenous urography in these boys. This may reveal such rarities as an ectopic ureter opening into the vas deferens.

Our findings suggest that a routine urogram in an otherwise asymptomatic patient under the age of 50 years is unnecessary. The urographic evidence suggests that, over this age, a pool of potentially infected urine is present in many cases and that sufficient abnormalities were found to justify a urogram in this group.

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Scrotal Lipomatosis

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Summary—The anatomy of scrotal fat was studied histologically and by dissection in 28 normal cadavers and 44 idiopathic infertile subjects. Two fat patterns were described: normal and infertile. In the normal pattern, a small posterior extratunicary pad of fat was constantly encountered. Intratunicary fat occurred as small granules between the cord veins.

Thirty-eight of the 44 idiopathic infertile subjects had scrotal lipomatosis, of which 2 types were recognised: extratunicary and intratunicary. The latter showed 2 patterns: diffuse and lobular. The diffuse pattern occurred in obese subjects and those of normal build, and the fat was firmly adherent to the cord veins. The lobular pattern occurred exclusively in the obese, and the lobules were loosely connected to the cord.

The anatomical features of the normal fat pattern in relation to maximal testicular thermoregulatory efficiency were discussed. The role of scrotal lipomatosis in infertility was clarified and the relationship of scrotal lipomatosis to obesity presented.

The role of scrotal fat in infertility has received little attention in the literature, probably because of the lack of information regarding its anatomical and pathological aspects. Moore and Quick (1924) showed that if the scrotum was enclosed in woollen material, the seminiferous tubules degenerated. Davidson (1966) believed that in obese subjects, the excess fat within the pelvis and the spermatic cord may be responsible for varicocele. He stated that if these patients were explored surgically, there would be excess cord fat and they would have to lose fat to improve their fertility.

In an attempt to provide a sound basis for these observations, and to assess the role of scrotal fat in male infertility, the scrotal fat pattern in both normal and infertile subjects has been studied. The results are now presented.

Material and Methods

The material comprised 2 groups. Group A consisted of 28 cadavers with normal scroti. Ten were full mature neonatal fetal deaths and 18 were fertile adults with an average age of 39 years. As each scrotal compartment was studied separately, this constituted 56 specimens. Twelve adults were of normal build and 6 were obese.

Specimens were studied histologically and by direct dissection. For dissection, the spermatic cord and testicle were exposed through an inguinoscrotal incision. The scrotal wall, fasciomuscular tube, cord veins and testis were examined for distribution of fat. Inguinal canal fat and its relation to scrotal and retroperitoneal fat were studied. A transverse suprapubic incision was then made and fat distribution in pubic and suprapubic areas was defined, emphasising its relation to scrotal fat.

For histological study, serial transverse cut sections were taken from the upper, middle and lower thirds of the cord. Skin strips were obtained from different parts of the scrotal sac. The material was examined microscopically for fat after being stained with haematoxylin and eosin and osmic acid.

Group B comprised 44 patients explored for idiopathic sterility. In this group the known causes of male infertility, as described by Dubin and Amelar (1971), were excluded. The average age was 35 years. Twenty-five patients were obese and 19 were normally built. They had been infertile for an average period of 12 years. The sperm count varied from azoospermia in 20 patients to below 20 million per ml in 24 patients.

In addition to routine clinical examination of the scrotum, the suprapubic area was examined for fat distribution and its relation to the scrotum. At operation the scrotal wall, fasciomuscular tube, cord veins and testis were examined for fat

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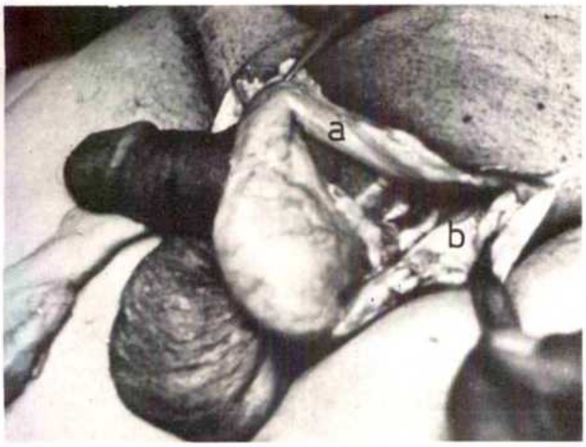

Fig. 1 Dissected scrotal cadaveric specimen showing the posterior extratunicary pad of fat: (a) spermatic cord, (b) posterior pad of fat.

distribution; a biopsy was taken from each, stained with haematoxylin and eosin and osmic acid and examined microscopically for fat.

Results

The results are presented for group A (normal fat pattern) and group B (infertile fat pattern).

Normal Fat Pattern

Of the 28 normal cadavers studied, no parietal or testicular fat could be detected either microscopically or by dissection. However, a small extratunicary patch of fat, consistently present in all specimens, was found to lie posterior to the cord, outside the fasciomuscular tube and lining the scrotal wall close to its neck (Fig. 1). It was triangular in shape with the base upward, and was continuous behind the cord and over the pubic ramus with the suprapubic fat.

No intertunicary fat could be identified. Intratunicary fat took the form, in all specimens examined, of small granules diffusely scattered between the cord veins, being denser in the lower portion of the cord. The fatty granules were fairly large in the obese subjects. Inguinal canal fat was also intratunicary in the form of small lobules that were more manifest close to the extraperitoneal tissue.

Suprapubic fat in the subjects of normal build was normally distributed, whereas in the obese it was thick but did not encroach on the scrotum or penis.

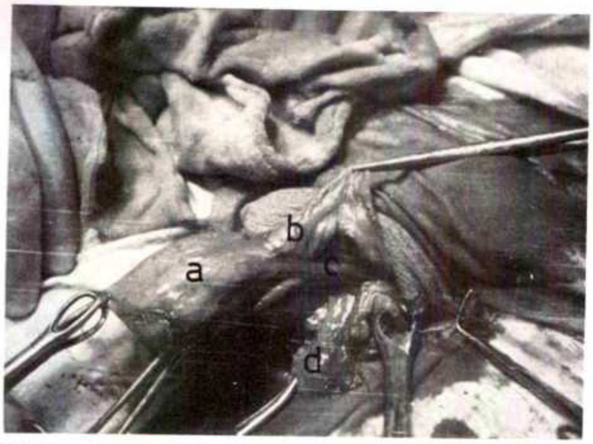

Fig. 2 Operative view showing normal fat pattern in idiopathic subfertile subject: (a) testis, (b) spermatic cord, (c) fasciomuscular tube opened, (d) posterior extratunicary pad of fat.

Infertile Fat Pattern

Of the 44 idiopathic sterile patients, 6 had a normal scrotal fat pattern; 5 of these were normally built and one was obese (Fig. 2). The remaining 38 patients showed excess and abnormally distributed scrotal fat, a condition I describe as "scrotal lipomatosis". Twenty-four patients were obese and 14 were normally built. The fat was funicular; no parietal or testicular fat was encountered.

Two types of scrotal lipomatosis could be identified: extratunicary and intratunicary. No intertunicary fat was detected either by naked eye or microscopically.

Extratunicary Lipomatosis Outside the fasciomuscular tube there was a thick pad of fat posterior to the cord in all patients (Fig. 3). It was

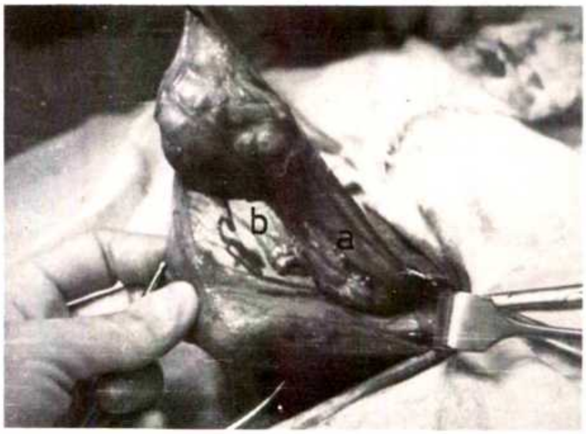

Fig. 3 Operative view of lobular lipomatosis showing the posterior extratunicary pad of fat containing tortuous veins: (a) spermatic cord, (b) extratunicary fat.

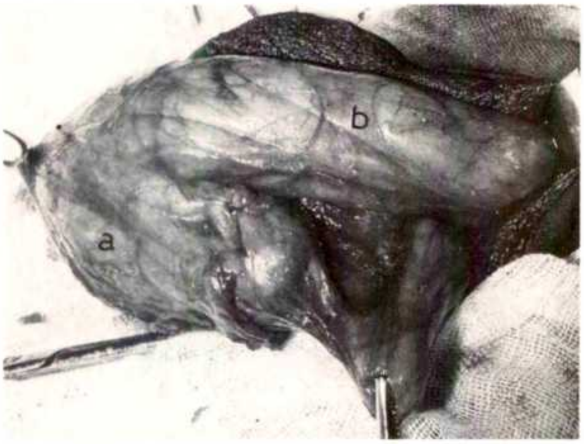

Fig. 4 Operative view showing diffuse lipomatosis of the spermatic cord extending down to cover the testis: (a) testis, (b) spermatic cord.

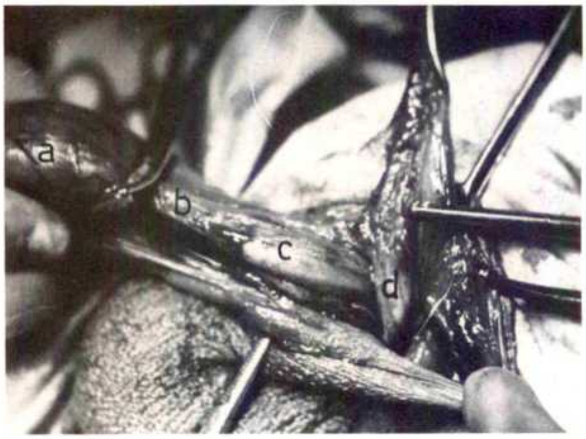

Fig. 5 Operative view showing lobular lipomatosis: (a) testis, (b) spermatic cord, (c) fat lobule, (d) posterior extratunicary pad of fat (dissected).

surrounded by a thin fascial layer and contained multiple small tortuous veins. It extended for a variable length along the cord from which it was easily separable, and appeared to be posterior extratunicary fat of the normal pattern which had become extremely thickened.

Intratunicary Lipomatosis After the fasciomuscular tube was opened, 2 patterns of fat distribution could be identified: diffuse and lobular.

(1) *Diffuse pattern.* The fat took the form of a diffuse sheet of variable thickness which covered the cord veins completely (Fig. 4). It was surrounded by a thin glistening capsule. The cord veins could not be identified through the fat which covered the separate pampiniform veins. The fat was so firmly adherent to the veins that dissection was difficult.

The diffuse fat pattern was encountered in 24 patients, 14 normally built and 10 obese. In 21 patients the fat was confined to the spermatic cord. In the remaining 3 patients it extended along the cord down to cover the anterior aspect and sides of the testis, overlying the *tunica vaginalis*, the epididymis being spared (Fig. 4). The fat was so adherent to the *tunica vaginalis* that its dissection necessitated excision of the parietal layer of the tunica. The 3 patients were normally built.

Of the 24 patients with a diffuse fat pattern, 13 were azoospermic, whereas the remainder had varying degrees of oligozoospermia. The testes were normally located in the scrotum in 17 patients, while in 7 there was bilateral scrotal redundancy more manifest on the left side. The testes were of normal size in 15 patients and small in 9, of whom 7 were normally built and 2 were obese. Testicular consistency was softer than normal in all cases. The suprapubic fat distribution was normal, though excessive in the obese patients.

(2) *Lobular pattern.* The intratunicary fat took the form of big pyriform lobules, each covered by a thin shiny capsule. The lobules lay on the outer aspect of the cord veins under cover of the internal spermatic fascial tube (Fig. 5). Unlike the diffuse pattern, they did not extend between the cord veins and were easily separable from them. Small fat granules similar to those of the normal fat pattern were scattered between the cord veins. The lobules varied in size and number, being larger and more numerous in the obese subjects. Each lobule had a pedicle which could be traced along the inguinal canal to the extraperitoneal fat. The pedicles gathered in the inguinal canal to form a "lipomatous cord" which could be traced up to the extraperitoneal tissue. This cord was found to attach the spermatic cord and testicle to the abdomen, and when sectioned the testis dropped to its normal position in the scrotum.

The lobular pattern occurred in 14 patients, all of whom were obese. Seven patients were azoospermic. The testes were of normal size in 8 patients and small in 6. Testicular consistency was softer than normal in all cases. Suprapubic fat was excessive and abnormally distributed. It bulged forward and downward, encroaching on the scrotum and penis. The testes were located high in the scrotum and in some cases were embedded in the suprapubic fat.

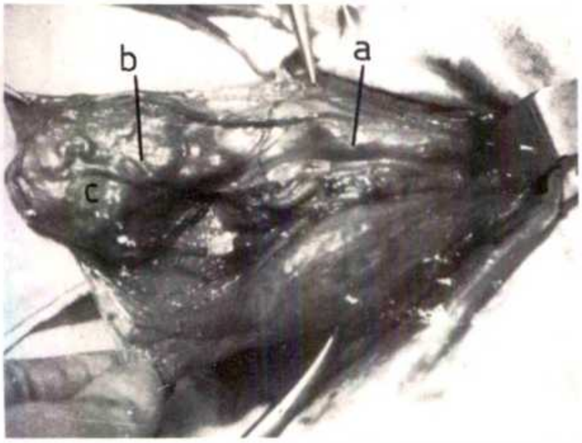

Fig. 6 Operative view showing cremasteric and pampiniform varicosity in subfertile subject with lobular lipomatosis. Extratunicary and intratunicary fat were removed: (a) pampiniform varices, (b) cremasteric varices, (c) testis.

Cord Varicosity

In the 38 cases of scrotal lipomatosis, the cremasteric veins were dilated and tortuous; pampiniform varicosity was also present in 20 patients; 13 of these had lobular lipomatosis and 7 had the diffuse pattern (Fig. 6). There were also dilated veins in the extratunicary and intratunicary fat (Fig. 3). Cord varices were not palpable clinically, being masked by lipomatosis. However, in 7 patients with diffuse lipomatosis there was scrotal redundancy, which would indicate cord varicosity.

Discussion

These results could shed some light on the role of scrotal fat in testicular thermoregulation and spermatogenesis.

The normal scrotal fat pattern has special features which provide maximum efficiency for the temperature regulating mechanism of the testis. Thus the absence of parietal fat allows the dartos to react to minimal temperature variations and facilitates changes in size of the scrotal sac. The lack of intertunicary fat indicates a high cremasteric sensitivity to different temperatures as well as increasing the efficiency of the fasciomuscular tube in pumping the blood up the cord. The intratunicary fat, being scanty, allows a free cord and the testicular mobility necessary for maintaining a constant scrotal-rectal temperature difference under varied environmental temperatures. Moreover, it does not interfere with either heat radiation or the fasciomuscular pump. However, the posterior extratunicary pad of fat seems to serve a double function: (*a*) it forms a cushion to protect the cord from being compressed by the underlying pubic bone, and (*b*) it insulates the cord from the heat radiated from the perineum and thigh.

Scrotal Lipomatosis and Subfertility

In the 44 cases of idiopathic sterility, scrotal lipomatosis was encountered in 86%, of which 63% were obese. Thirty-seven per cent were of the lobular pattern (which occurred exclusively in the obese), while 63% were of the diffuse pattern, of which 42% were obese.

The high incidence of scrotal lipomatosis in sterile patients indicates a relationship between them. Scrotal lipomatosis seems to inhibit spermatogenesis in the following ways:

(1) Insulation: fat acts as an insulator which interferes with heat radiation and testicular aeration.
(2) Compression: the excess intratunicary fat, being enclosed within the rigid internal spermatic fascial tube, compresses the cord veins; this leads to venous back pressure and testicular congestion. This is shown by the high incidence of cord varices in scrotal lipomatosis.
(3) Testicular ischaemia: increased tension within the fasciomuscular tube as a result of lipomatosis and cord congestion may lead to testicular artery compression and ischaemia. Both testicular congestion and ischaemia would explain the high incidence of small and soft testes in lipomatosis.
(4) Inefficient venous pumping: the fasciomuscular tube acts as a pump whereby the blood is pushed up the cord to the abdomen, the cremasteric muscle being the important component of the pump (Shafik *et al.*, 1972; Shafik, 1973a). Excess intratunicary fat would interfere with the efficiency of the pumping mechanism, resulting in venous stasis and testicular congestion.
(5) Cord suspension: the "lipomatous cord" suspends the testis to the warm abdomen and interferes with its mobility in relation to temperature variations. The testis may be highly suspended to lie close to the external inguinal ring, simulating the high scrotal undescended testis. This was especially manifest in obese patients in whom the testes were embedded in the excess redundant suprapubic fat.

Scrotal Lipomatosis and Obesity

In the present series, 63% of patients with scrotal lipomatosis were obese; such a high incidence points to a relationship between these conditions.

In the obese, excessive cord fat could result from

(*a*) an exaggeration of the normal fat pattern, the cord sharing with the body the generalised obesity; it seems most likely that this is the cause of the diffuse fat pattern which occurred in 42% of the obese; (*b*) extraperitoneal fat herniation through the inguinal canal to the scrotum. This would explain the lobular lipomatosis which occurred exclusively in the obese; the lobules could be traced along their pedicles to the extraperitoneal fat.

While the origin of scrotal lipomatosis can be explained in the obese, it is uncertain in the normally built subjects, 37% of whom had lipomatosis. It could be the result of a chronic inflammatory process of the spermatic cord stimulating a hyperplastic response in the normal cord fat, a condition analogous to perinephric lipomatosis of the chronically inflamed kidney. The cord fat compresses the cord veins and causes secondary varicosities. This is supported by the fact that scrotal lipomatosis in subjects of normal build is exclusively of the diffuse pattern, the fat of which is adherent to the spermatic cord and would indicate an inflammatory process.

Scrotal Lipomatosis and Cord Varicosity

Cord varices were present in all cases of lipomatosis due to venous stasis, the result of compression of the veins by the intratunicary fat as well as a disordered venous pumping mechanism. It could be argued that cord lipomatosis is secondary to varicosities of the spermatic cord. Against this is the fact that, at operative correction of primary varicoceles, no lipomatosis is encountered even in the most advanced varicoceles.

The degree of varicosity varies with the amount of intratunicary fat. Two types of varices were encountered: cremasteric and pampiniform. Cremasteric varicosity occurred in all cases of lipomatosis since cord congestion is manifest primarily in the cremasteric veins as they lie outside the internal spermatic tube and are poorly-muscularised (Shafik, 1973b). Increasing venous congestion causes dilatation of the pampiniform veins.

Scrotal redundancy in diffuse lipomatosis is due to cord varicosity. However, it is not evident in lobular lipomatosis, despite cord varicosity, as the testis is being supported by the lipomatous cord.

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Lipectomy in the Treatment of Scrotal Lipomatosis

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Summary—Scrotal lipectomy was performed in 102 infertile patients with scrotal lipomatosis; suprapubic lipectomy was included in 22 patients who had redundant suprapubic fat.

Improvement in semen quality was obtained in 64.7% and pregnancy occurred in 19.6%. Statistically, the improvement was significant in both the sperm count and motility of the total series and only in the sperm count in the cases which produced pregnancy. The technique is described and the factors to which the results may be attributed are discussed.

In a recent study it was suggested that scrotal lipomatosis plays a significant role in the pathogenesis of male infertility (Shafik and Olfat, 1980). Two types of scrotal lipomatosis are recognised: extratunicary and intratunicary, according to the relation of the fat to the fasciomuscular tunics of the spermatic cord.

Scrotal lipomatosis may inhibit spermatogenesis through various mechanisms (Shafik and Olfat, 1980). The insulating action of fat interferes with local testicular temperature. The excess intratunicary fat may compress the veins of the cord, resulting in testicular congestion. Lipomatosis and cord congestion may even compress the testicular artery and lead to testicular ischaemia. The lipomatous cord holding the testis to the warm abdomen interferes with its mobility in response to temperature variations. Finally, the excess suprapubic fat may disturb the testicular thermoregulatory mechanism.

Experimentally, Moore and Quick (1924) showed that if the scrotum was enclosed in woollen material, the seminiferous tubules degenerated. Similarly, Phillips and McKenzie (1934), in their experiment on rams, showed that heat insulation of the scrotum caused severe degenerative changes in the testes, and that although recovery was possible, some permanent damage remained.

Thus there is a possibility that the treatment of scrotal lipomatosis in infertile patients could improve spermatogenesis, especially in early cases before irreversible testicular damage occurs.

Attempts to lose sufficient body fat by diet and medication alone have failed to improve the semen quality. These methods are exhausting, time-consuming and most patients fail to maintain the strict regimen. Furthermore, scrotal lipomatosis can occur not only in obese subjects but also in patients of normal build (Shafik and Olfat, 1980). For these reasons, surgical removal of the excess scrotal fat was thought to be the appropriate treatment for scrotal lipomatosis.

This paper presents the technique and results of scrotal lipectomy.

Material and Methods

Scrotal lipectomy was performed in 102 infertile patients with scrotal lipomatosis; suprapubic lipectomy was also done in 22 patients with excess suprapubic fat. Azoospermic patients with scrotal lipomatosis were not subjected to lipectomy. Average age was 38 years: 74 patients were obese and 28 were of normal build.

Scrotal lipomatosis presents with a characteristic clinical picture. The spermatic cord is thick, pulpy and feels matted, though soft in consistency. The different constituents of the spermatic cord cannot be rolled freely, being wrapped and impregnated with fat. The extratunicary pad of fat, which is normally small, is felt as a large, soft, lobulated mass posterior to the cord, close to the scrotal neck. Testicular position is variable. In normally built subjects, the testes are normally located within the scrotum, though they may be lowered because of the accompanying varicosities. In the obese, the testes lie either close to the scrotal neck or are embedded within the bulky suprapubic fat.

Pre-operatively all patients were fully examined to exclude other causes for infertility and had

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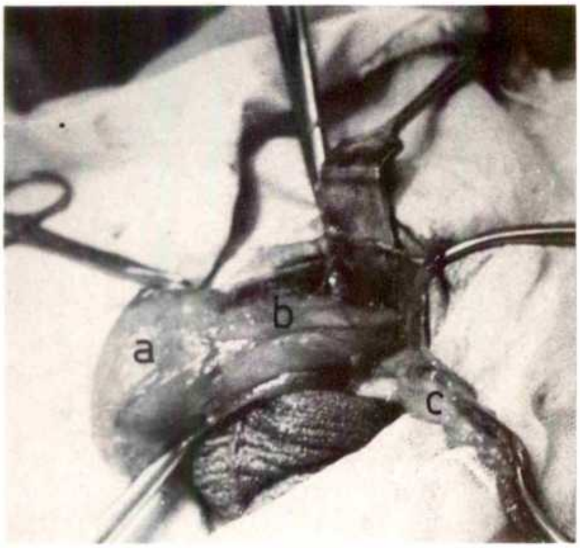

Fig. 1 Operative view of infertile patient with diffuse cord lipomatosis showing the posterior extratunicary pad of fat dissected free. a: testicle, b: spermatic cord with diffuse lipomatosis, c: pad of fat.

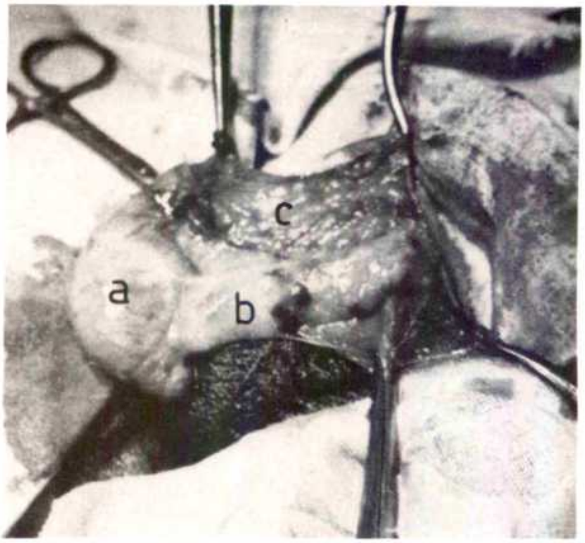

Fig. 2 Same patient after excision of posterior extratunicary fat and opening the fasciomuscular tube to expose cord fat. a: testicle, b: spermatic cord with diffuse lipomatosis, c: fasciomuscular tube opened.

normal thyroid, adrenocortical and pituitary gonadotrophin function tests (Dubin and Amelar, 1971).

At least 3 semen specimens from each patient were checked pre-operatively; all had varying amounts of oligozoospermia and most of them showed severely impaired motility (Table 1*). There were abnormal sperm forms in 35.3% of the cases.

All patients had been unsuccessfully treated medically for at least 4 years before the operation. They were followed up for at least 18 months after surgery.

Technique of Lipectomy

A longitudinal incision was made in the anterior aspect of the upper half of the scrotal skin. The testis and spermatic cord were delivered outside the scrotum and the posterior extratunicary pad of fat was dissected and excised (Fig. 1). The fasciomuscular tube was then opened longitudinally and the intratunicary fat dissected free of the veins and removed, avoiding injury to the testicular artery (Figs. 2 and 3). The lobular fat was found easier to dissect than the diffuse type, which was firmly adherent to the cord veins.

In 6 patients, intratunicary fat extended down the cord to cover the front and sides of the testis, overlying the *tunica vaginalis*, the epididymis being spared (Fig. 4). The fat was adherent to the *tunica vaginalis*, so that its dissection necessitated excision of the parietal layer of the tunica.

Special attention was paid to the "lipomatous cord" extending from the retroperitoneal tissue, along the spermatic cord in the inguinal canal to the intratunicary fat in the scrotum. If present

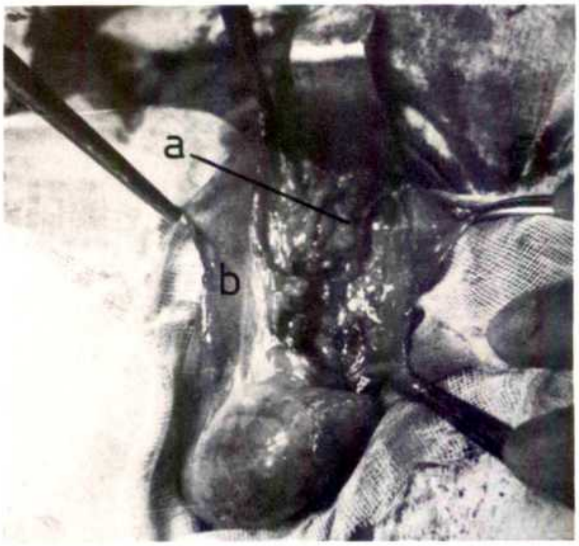

Fig. 3 Same patient after cord lipectomy showing cord veins free of fat. a: cord veins defattened, b: fasciomuscular tube.

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* Available from the Editor on request.

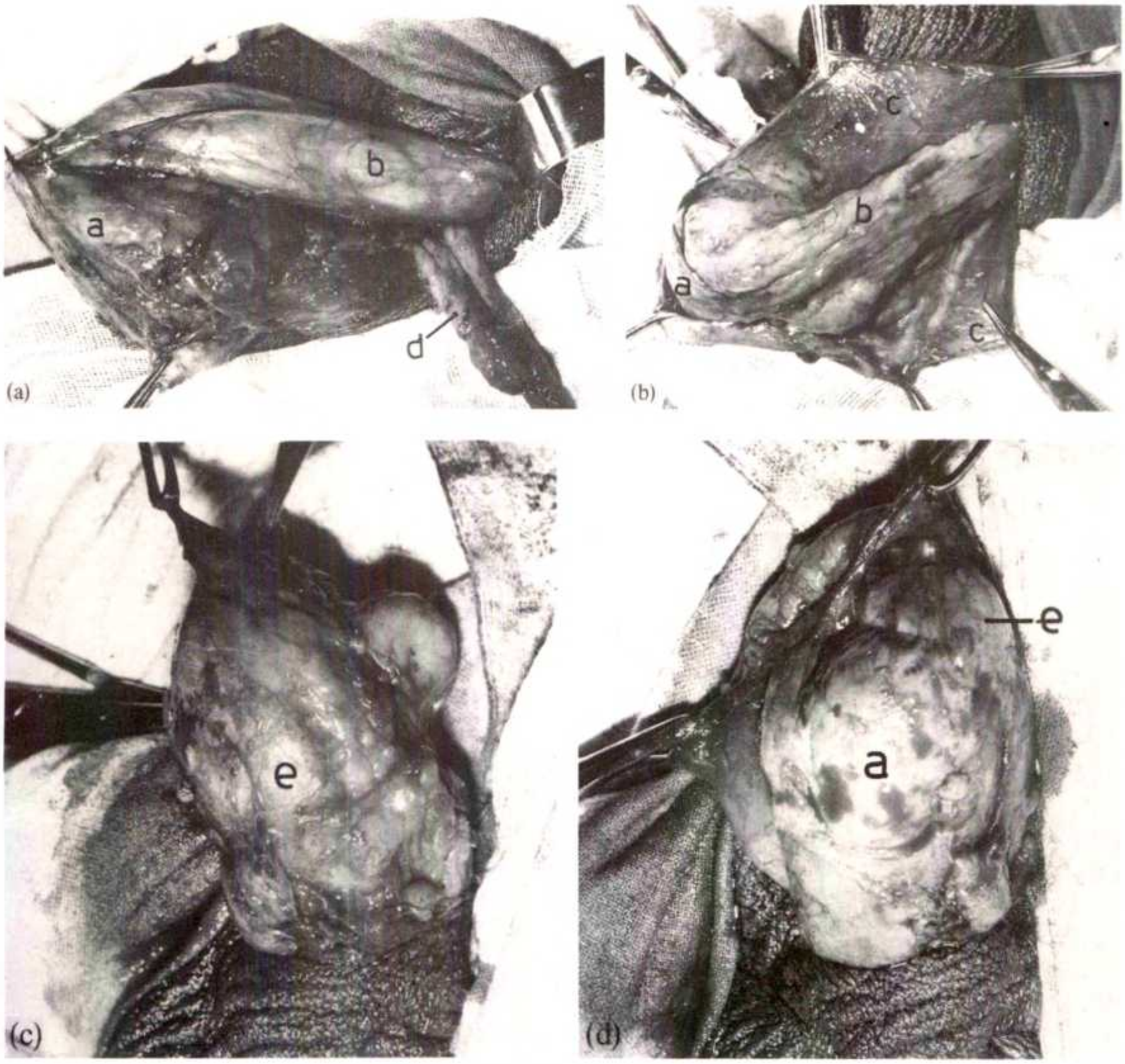

Fig. 4 Operative view showing diffuse lipomatosis of the spermatic cord extending down to cover the testis. (a) Extratunicary pad of fat dissected free. (b) Diffuse fat after fasciomuscular tube has been opened. Observe fat extending over testis. (c) Fat covering front and sides of testis (anteroposterior view). (d) Dissection of fat over testis.
a: testicle, b: spermatic cord, c: fasciomuscular tube opened, d: extratunicary pad of fat dissected free, e: fat over testis.

(as indicated by the high position of the testis in obese subjects), it was excised. In such a case the scrotal incision was extended into the inguinal area, the external oblique and the fasciomuscular tube were incised to open the inguinal canal and expose the spermatic cord, and the lipomatous cord was dissected free of the cord veins and excised.

At the end of the operation, the veins of the cord should be clear of fat and the testis should lie in the most dependent part of the scrotum. If the fasciomuscular tube was capacious and the veins varicose, tubal overlapping or plication was performed (Shafik, 1972). Finally, the wound was closed with drainage and the scrotum was held to the abdomen by a stitch for 48 h. This technique was then used on the other side of the scrotum at the same operation.

When the suprapubic fat was excessive and so redundant that it encroached on the scrotum, suprapubic lipectomy was also done. A transverse elliptical suprapubic incision was made to include the redundant skin and the excess fat. The suprapubic fat was dissected down to the rectus sheath on both sides and excised. The 2 testes were then delivered through the same incision and cord

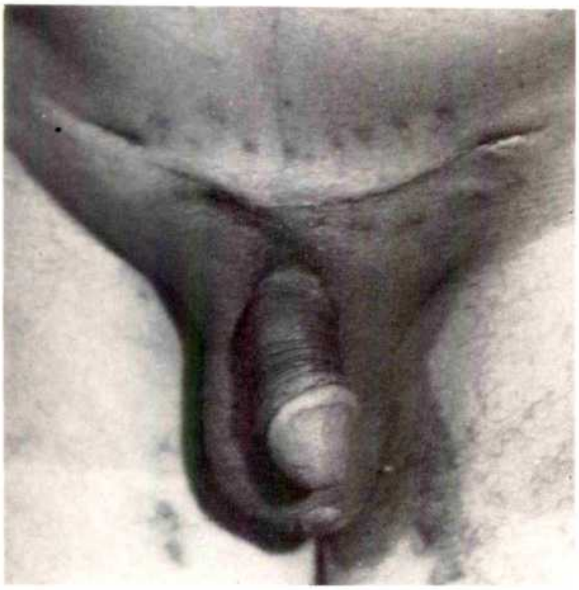

Fig. 5 Patient 4 weeks after suprapubic and cord lipectomy.

Table 2 Result of Lipectomy in 102 Patients with Scrotal Lipomatosis

Patients and wives	*No.*	*(%)*
Total no.	102	—
No. with improved semen quality	66	64.7
No. of pregnancies	20	19.6

defattening performed as above. The suprapubic wound was then closed with drainage (Fig. 5).

Results

The post-operative course was uneventful. In 4 patients treated with suprapubic lipectomy, suprapubic haematoma and infection soon cleared with free drainage and antibiotics.

The results of lipectomy in 102 patients with scrotal lipomatosis are shown in Table 2. Improvement in semen quality occurred in 66 cases, while 20 cases produced pregnancy (Table 3). The pre-operative and post-operative sperm count, motility and morphology in the 66 improved patients and in the 20 patients producing pregnancy are shown in Tables 4 and 5. The semen quality in the 36 unimproved patients is shown in Table 6.

Statistical analysis of the semen character of the total series according to the method of Fisher (1946) showed a significant post-operative increase in both sperm count and motility (Table 7). Although the abnormal sperm forms showed a post-operative decrease, this was not statistically significant. Semen volume showed a slight post-operative increase.

Statistical analysis of patients whose wives became pregnant (Table 8) showed a significant post-operative increase in the sperm count only.

Table 3 Semen Characteristics of 20 Patients with Scrotal Lipomatosis who Produced Pregnancy after Lipectomy

Case	*Before operation*				*After operation*			
	Volume (c.c.)	*Count million per ml.*	*Motility (%)*	*Abnormal forms (%)*	*Volume (c.c.)*	*Count million per ml*	*Motility (%)*	*Abnormal forms (%)*
1	4.1	19.4	70	30	4.3	61.6	70	15
2	2.2	19.6	0	25	2.9	53.8	72	8
3	2.0	15.0	5	26	4.1	58.4	76	22
4	4.0	15.0	85	15	4.1	56.4	78	18
5	3.1	9.3	26	30	2.4	46.0	78	16
6	3.0	10.5	45	60	2.8	51.4	76	18
7	2.5	18.5	30	30	3.0	46.0	68	22
8	4.2	13.6	30	18	4.0	84.6	69	22
9	2.8	14.8	35	20	3.0	58.2	78	16
10	3.0	12.0	80	10	2.8	41.0	78	10
11	2.8	12.6	35	23	3.5	42.5	72	18
12	1.2	14.6	10	22	2.8	51.8	68	20
13	2.2	16.8	20	28	2.5	48.0	68	12
14	2.9	13.0	0	25	3.0	48.4	70	24
15	3.5	14.0	25	20	4.2	42.0	78	18
16	3.1	18.5	45	35	4.1	46.0	78	22
17	5.2	8.6	27	14	4.6	45.2	78	14
18	4.1	12.5	38	46	3.6	62.2	70	26
19	3.0	4.8	30	36	4.0	46.0	75	14
20	3.0	12.0	75	30	4.0	62.0	72	20

Table 4 Sperm Count, Motility and Morphology in 66 Improved Patients

Time of test	*No. of patient with sperm count (milllion/ml) of*											
	0.3-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	*100+*
Before operation	9	15	42									
After operation		1	8	10	14	21	8	3		1		
Time of test	*No. of patients with motility (%) of*											
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	
Before operation	7	2	14	17	12	7	2	2	2	1		
After operation			4	6	7	4	3	17	24	1		
Time of test	*No. of patients with percentage of abnormal forms of*											
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	
Before operation	1	1	13	34	7	5	2	1	1	1		
After operation	1	2	25	29	6	1	1	1				

There was a post-operative improvement in sperm motility, but this was not significant because of the high pre-operative standard deviation in these cases. Two cases with 0% motility and one case with 5% motility before operation showed marked post-operative improvement to 72, 70 and 76% respectively (Table 3). The semen volume showed a slight increase after surgery.

Discussion

The effectiveness of lipectomy in the treatment of infertile patients with scrotal lipomatosis is demonstrated in the present study. Improvement in semen quality occurred in 64.7%, while 19.6% produced pregnancy.

The improvement which follows lipectomy could be attributed to:

(1) Normal testicular thermoregulation due to removal of the fat which acts as an insulator.

(2) Fasciomuscular tube decompression which releases the tension from both the cord veins and testicular artery. Testicular decongestion and arterialisation could thus be achieved.

(3) Improved fasciomuscular pump efficiency as a result of tubal decompression.

Table 5 Sperm Count, Motility and Morphology in 20 Patients who Produced Pregnancy

Time of test	*No. of patients with sperm count (million/ml) of*											
	1-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	*100+*
Before operation	1	2	17									
After operation						10	6	3		1		
Time of test	*No. of patients with motility (%) of*											
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	
Before operation	3	1	1	6	3	2		1	2	1		
After operation								7	12	1		
Time of test	*No. of patients with percentage of abnormal forms of*											
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	
Before operation		1	5	10	2	1	1					
After operation		2	12	6								

(4) Lipomatous cordectomy which allows free testicular mobility in response to temperature variations.

(5) Tubal overlapping or plication, which helps testicular decongestion by establishing an efficient fasciomuscular pump that supports the varicose cord veins which may result from the lipomatosis compression (Shafik and Olfat, 1980).

The operation is simple and radical defattening of the cord is achieved without subjecting the patient to a strict and prolonged dietetic regime.

Table 6 Sperm Count, Motility and Morphology in 36 Unimproved Patients

Time of test	*No. of patients with sperm count (millions/ml) of*											
	0.7-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*	*100+*
Before operation	15	5	16									
After operation	14	5	17									

Time of test	*No. of patients with motility (%) of*										
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*
Before operation	6	3	7	5	7	3	3	1	1		
After operation	2	1	5	10	1	6	9	1	1		

Time of test	*No. of patients with percentage of abnormal forms of*										
	0-5	*6-10*	*11-20*	*21-30*	*31-40*	*41-50*	*51-60*	*61-70*	*71-80*	*81-90*	*91-100*
Before operation			6	12	8	4	4	1		1	
After operation			7	20	5	3	1				

Table 7 Statistical analysis of the semen characteristics of 102 Patients with Scrotal Lipomatosis Before and After Lipectomy

No. of cases		*Before operation*				*After operation*			
		Volume (cc.)	*Count million per ml*	*Motility (%)*	*Abnormal forms (%)*	*Volume (cc.)*	*Count million per ml*	*Motility (%)*	*Abnormal forms (%)*
	M	3.3	10.5	29.5	32.5	3.4	27.9*	47.03*	25.3
102	SD	±0.86	±5.4	±19.1	±15.1	±0.67	±18.6	±22.9	±9.8

* Statistically significant when compared with those before operation.
M = Mean.
SD = Standard deviation.

Table 8 Statistical Analysis of the Semen Character of the 20 Patients with Scrotal Lipomatosis who Produced Pregnancy after Lipectomy

No. of cases		*Before operation*				*After operation*			
		Volume (cc.)	*Count million per ml*	*Motility (%)*	*Abnormal forms (%)*	*Volume (cc.)*	*Count million per ml*	*Motility (%)*	*Abnormal forms (%)*
	M	3.1	13.8	35.6	27.2	3.5	52.6*	73.6	17.8
20	SD	±0.91	±3.8	±25.2	±11.38	±0.69	±10.2	±4.04	±4.7

* Statistically significant when compared with those before operation.
M = Mean.
SD = Standard deviation.

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A Double-blind Trial of Half-strength Polybactrin Soluble GU Bladder Irrigation in Cystoscopy

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Summary—In an attempt to reduce post-cystoscopy urinary tract infection half-strength Polybactrin Soluble GU solution was used as the bladder irrigating fluid. Although the infection rate was markedly reduced, this just failed to be significant. However, it is believed that with a better combination of antibiotics the incidence of post-cystoscopy urinary tract infection can be significantly reduced.

Urinary tract infection after single instrumentation of the bladder is reported to occur in up to 7% of cases (Kass, 1957; Lytton, 1961; Higgins, 1966; Walter and Vejlsgaard, 1978). Urethral instrumentation is so commonly performed that the total incidence of urinary infection following this procedure represents a significant complication.

The urethra in both males and females is colonised by bacteria (Helmholz, 1950; Scardino *et al.*, 1973; Stamey, 1973) and it is inevitable that these organisms will be introduced into the bladder with the passage of an instrument through the urethra (Guze and Beeson, 1956). Although bacterial contamination of the bladder by urethral organisms is difficult to prevent, the normal bladder has considerable resistance to infection (Cox and Hinman, 1961; O'Grady and Cattell, 1966) and spontaneous disappearance of bacteria after instrumentation is common (Clarke and Joress, 1960). Nevertheless, post-instrumentation infection does occur.

Systemic prophylactic antibacterial therapy after instrumentation of the urinary tract has been used in an attempt to reduce post-instrumentation infection, but has failed to show any benefit (Higgins, 1966; Blackard and Nicolaidis, 1972). In the present study we have attempted to reduce post-cystoscopy urinary tract infection by the use of the antibiotic solution in the bladder irrigating fluid at cystoscopy. Since the purpose of the regime was prophylaxis against possible contamination rather than treatment of an established infection, half-strength rather than full-strength Polybactrin Soluble GU was considered adequate in terms of antibiotic concentration (Kucers and Bennett, 1979) and was to be preferred in terms of cost.

Patients and Methods

All patients entering hospital for cystoscopy over the trial period were eligible for inclusion in the study. Any patient who had an indwelling catheter left *in situ* following cystoscopy was excluded from the trial, as was any patient with infected urine on admission. The patient's informed consent to the trial was obtained.

Pre-operatively, a mid-stream specimen of urine (MSU) was taken for bacterial analysis. The patients were randomly allocated to either the control group or the treatment group by the theatre sister preparing a colour coded irrigating solution for random operating lists. The composition of the fluid given to each group was known only by the theatre sister. For the treatment group 6 vials of Polybactrin Soluble GU containing a total of 450,000 units of polymyxin B sulphate, 120,000 units of neomycin sulphate and 6000 units of bacitracin were added to each bag of the irrigating fluid (either 1.5% glycine urological solution or 0.9% sodium chloride solution contained in 3-litre bags). For the control group of patients no antibiotic solution was added. Before introduction of the cystoscope the genitalia were cleaned with Savlon. A sample of urine was obtained and sent for bacteriological analysis. The bladder was then filled with the irrigating fluid to allow inspection and the cystoscopy was completed with per-urethral diathermy of bladder tumours when necessary. More than one irrigation was occasion-

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ally required because bleeding obscured the view through the cystoscope. On the morning after the cystoscopy a further mid-stream sample of urine was taken.

After discharge the patient was asked to provide dip slides on the third, seventh and fourteenth day after cystoscopy. These were sent to the laboratory by first class evening post, the average transit time being about 16 h. The patient was also informed of the symptoms of urinary tract infection and requested that should he develop any of these symptoms, he was to provide a mid-stream specimen of urine as described above and send this to the laboratory. In the event, this was not necessary, for whenever a possible infection was indicated by the bacteriological results the patient was at once visited at home, details of any urinary symptoms noted and a further mid-stream specimen of urine collected and analysed. Thus the transit time of the mid-stream specimens from the patient's home was one hour before the specimen was refrigerated.

Bacterial growth occurring on the dip slides was described as confluent, semi-confluent or moderate. A confluent or semi-confluent growth of bacteria on the dip slides has been found to correlate with significant bacteriuria (Guttman and Naylor, 1967; McAllister *et al.*, 1973).

In the laboratory the dip slides were incubated for 24 h. Confluent or semi-confluent bacterial growth was subcultured for identification in the same manner as for the mid-stream samples of urine cultures. Using a standard loop, urine from the mid-stream samples was inoculated on to cystine-lactose-electrolyte deficient medium and incubated for 24 h. The total bacterial count per ml was calculated from the colony count results. The organisms were identified using standard bacteriological methods. In addition, the urine specimens were examined microscopically and the white cell count determined.

Patients were considered to have a urinary tract infection if (1) there was a bacterial count greater than 100,000/ml of urine on a mid-stream sample of urine (Kass, 1957) and (2) there was a confluent or semi-confluent growth of organisms on the dip slides, together with symptoms of cystitis and a sterile pyuria on a subsequent mid-stream specimen of urine.

This latter definition of urinary infection was necessary because some patients had either received treatment for their urinary tract infection from their General Practitioner prior to sending in a mid-stream specimen of urine, or had failed to send in the specimen when they developed symptoms of a urinary tract infection. The organism isolated in the mid-stream sample of urine was taken as the infecting one. If the mid-stream specimen culture was sterile, as following treatment from the General Practitioner, the organism isolated on the dip slide was taken as the infecting one.

Table 1 Infection Rate in the Control and Treated Group

	Treated group		*Control group*	
	Infected	*Non-infected*	*Infected*	*Non-infected*
	3 (5.3%)	53	9 (16.6%)	47
Total	56		56	

Results

One hundred and twenty-two cystoscopies were performed on 112 patients (79 male and 33 female). Six of the cystoscopy results were removed from the trial because the patients failed to return sufficient dip slides or urine specimens, and 4 cases where the urine was infected on admission were also excluded. One hundred and twelve cystoscopy results have therefore been analysed. Ninety-four cystoscopies were carried out on patients with previous malignancy of the bladder (43 in the control group and 51 in the treatment group) and 18 were diagnostic cystoscopies (13 in the control group and 5 in the treatment group). The patients were closely matched, with the mean age of the control group being 66 years and that of the treatment group 64 years. Not all of the patients managed to return the dip slides on the days requested.

Nine of the 56 patients in the control group (16.6%) developed post-cystoscopy urinary tract infection, whilst 3 of the 56 patients in the treatment group (5.3%) developed this complication (Table 1). This reduction of the infection rate was marked, but just failed to reach statistical significance using the χ^2 test (χ^2 with Yates correction$=3$, $P<0.05$). Symptoms of urinary tract infection developed in 9% of cases in the control group and 1.7% in the treatment group. This reduction was also marked, but again failed to be statistically significant (Table 2). There was no significant difference in the incidence of infection between males and females.

Table 2 Incidence of Symptoms in Control and Treatment Groups

	Treated group	*Control group*
Symptoms	1	5
Total	56	56
Percentage	1.7	9

When infection did occur, only 6 of the 12 patients with bacteriologically proven infection developed symptoms, and of these patients 5 had received treatment. None of the 6 patients with bacteriologically proven infection without symptoms had received treatment (Table 3).

There was no significant difference in the infection rate between the cystoscopies with per-urethral diathermy for bladder tumours and those where no diathermy was undertaken (Table 4).

Ninety per cent of the urinary tract infections developed within 7 days of instrumentation, with 11 of the 12 presenting during the first post-cystoscopy week and only one infection developing in the second week. However, not all of the infections occurred immediately after instrumentation, for 40% presented on the sixth post-cystoscopy day or thereafter (Table 5).

In those patients who developed a urinary tract infection all mid-stream specimens of urine culture grew bacteria, except in those patients who had had treatment given to them by their General Practitioners for their infection. In these patients the infecting organism was identified from the dip slide cultures. It will be seen that in the treatment group of patients, the infecting organisms were all streptococci, whilst in the control group the organisms were predominantly *Escherichia coli*, a common urinary tract pathogen (Table 3).

The dip slides proved to be extremely accurate in demonstrating the presence or absence of a urinary tract infection in those cases where the dip slide result was followed by a mid-stream sample of urine analysis (Table 6). However, they were not accurate in determining the infecting organism, for where no antibiotics were given by the General Practitioner the organisms grown on the dip slide and from the mid-stream sample were the same in only 60% of cases (Table 3).

Four patients had infected urine when admitted and they were excluded from the trial. However, they were studied in the usual manner to see what result could be found. Two patients fell into the control group and 2 into the treatment

Table 3 Bacteriology of the Infected Urine Specimens

Dip slide	*MSU*	*Symptoms*	*Treatment*
Control group			
Semi-confluent mixed growth	WBC=200, ct=100,000+ *Staph. albus*	No	No
Confluent growth *Staph. aureus*	WBC=0, ct=100,000+ *Staph. albus*	No	No
Moderate growth *Proteus mirabilis*	WBC=1600, ct=100,000+ *Proteus mirabilis*	Epididymo-orchitis	Yes
Confluent growth *Esch. coli*	WBC=20, ct=less than 5000 No growth	Yes	Yes
Semi-confluent growth *Esch. coli*	WBC=40, ct=less than 5000 No growth	Yes	Yes
Semi-confluent staphylococci/streptococci	WBC=10, ct=100,000+ mixed coliforms	Yes	No
Confluent growth *Esch. coli*	WBC=0, ct=100,000+ *Esch. coli*	No	No
	WBC=320, ct=100,000+ mixed coliforms	Yes	Yes
Confluent growth *Esch. coli*	WBC=80, ct=100,000+ *Staph. albus*	No	No
Treatment group			
Confluent growth Group D streptococcus	WBC=40, ct=less than 5000 No growth	Yes	Yes
	WBC=10, ct=100,000+ streptococcus D	No	No
Semi-confluent growth Group B streptococcus	WBC=0, ct=100,000+ streptococcus B	No	No

ct = bacterial count.

Table 4 Infection Rate in Diathermy and Non-diathermy Cystoscopies

	Diathermy cystoscopy		*Simple cystoscopy*	
	Control	*Treatment*	*Control*	*Treatment*
Infected	6	2	3	1
Non-infected	28	30	19	23
Percentage infected	21.4	6.2	15.7	4.2

group. All of the patients subsequently cleared their urine of bacteria and the treatment failed to confer any advantage in speed of clearance.

Discussion

The normally quoted figures for urinary tract infection after single instrumentation in patients with otherwise healthy urinary tracts are 1 to 7% (Kass, 1957; Lytton, 1961; Higgins, 1966; Walter and Vejlsgaard, 1978). These figures, however, are based upon the results of solitary post-instrumentation urine specimen cultures taken at isolated times within the first post-instrumentation week. In the present trial a more detailed search for infection has been made in an attempt to obtain an accurate incidence of post-instrumentation infection, with 4 serial urine samples being examined over a 2-week period after the cystoscopy (see Patients and Methods). Since 3 of the 4 post-cystoscopy urine samples were to be given after the patient's discharge from hospital, dip slides were used as a screening test since it has been shown that they are accurate in detecting urinary tract infections (Guttman and Naylor, 1967; McAllister *et al.*, 1973). This technique was backed up by MSU analysis where infection was suspected from the dip slide results. In this trial, the dip slide results which were followed up by an MSU culture showed an accurate prediction of urinary tract infection. However, there was little correlation between the organisms grown on the dip slides and those from the mid-stream samples of urine. This inaccuracy did not appear to be due to an excessive transit time of the dip slides or MSU, as dip slide cultures do not deteriorate for up to 5 days (McAllister *et al.*, 1973), and MSU results are accurate when refrigerated up to 24 h (Craig, 1963). Normally, dip slides are accurate in growing the infecting organism in the urine (McAllister, 1979; personal communication), and it is most likely that this discrepancy between the dip slide and MSU results stems from the fact that 36 to 48 h had elapsed between the urine being passed for the dip slide and the MSU analyses. Furthermore, any sampling system is at the mercy of the quality of the urine specimen obtained, and the discrepancy may reflect the fact that with the doctor being present, more care was taken by the patient in the collection of the MSU than in the collection of the dip slide when no doctor was present. This discrepancy does not invalidate the findings of the high incidence of urinary tract infection, for it must be remembered that the back-up MSU was included in the study to confirm the dip slide findings of an infection, and in this function the MSU results were accurate.

Table 5 Percentage Infection Rate/Time After Cystoscopy

	Treatment group		*Control group*	
	No. of cases	*Percentage infection*	*No. of cases*	*Percentage infection*
Day 1	1	1.8	1	1.8
2	1	3.5	1	3.5
3			3	8.9
6	1	5.3	1	10.7
7			2	14.2
14			1	16.6

Table 6 Prediction of Urinary Infection by Dip Slides Compared with MSU

	Dip slide growth	*Correlation with MSU growth*		
		Correct	*Incorrect*	*Percentage agreement*
Infected	Confluent	5	0	100
	Semi-confluent	6	0	100
Non-infected	Moderate growth	13	1	93

The results of this study have shown that if a detailed search is made for post-instrumentation urinary tract infection, the incidence of infection rises to 16%. However, only 50% of these patients with bacteriologically proven infection developed symptoms, a finding which has been confirmed by others (Dove *et al.*, 1972). The post-cystoscopy urinary infections were scattered throughout the 2 weeks of the study; 92% occurred in the first post-cystoscopy week, but just under 50% presented on the sixth post-cystoscopy day or thereafter. Bacteriological examination of the urine on the fourth post-instrumentation day only, as was done by Lytton (1961) and Higgins (1966), would have entirely missed the later infections, and a single urine analysis on the seventh post-instrumentation day only (Kass, 1957; Walter and Vajlsgaard, 1978) could well have missed the early urinary infections, since the urine might have spontaneously become clear of bacteria. It must be concluded, therefore, that the generally accepted figures of 1 to 7% post-instrumentation urinary tract infection rate are incorrectly low.

If, at the same time as organisms are introduced into the bladder by instrumentation, an antibiotic (or combination of antibiotics) could also be introduced in a concentration sufficient to destroy the bacteria, then it would appear possible to reduce significantly the incidence of post-instrumentation urinary tract infection. We have used half-strength Polybactrin Soluble GU solution as the bladder irrigating fluid, calculations having shown that the concentration of the constituent antibiotics in this diluted solution should be 10 times that of the minimum inhibitory concentration against the usual urinary pathogenic organisms (Meleney, 1956; Kucers and Bennett, 1979). However, the high initial concentration of antibiotic in the small amount of solution left in the bladder after cystoscopy is diluted by the accumulation of urine and its effectiveness thereby reduced. Nevertheless, the reduction of the post-cystoscopy infection rate from 16.6 to 5.3% would suggest that the necessary concentration of antibiotic can be obtained during the immediate post-cystoscopy period using this technique of bladder irrigation, and that the high concentration is maintained long enough to destroy the bacteria which have been introduced into the bladder. Whilst these results are encouraging, there were insufficient patients in the trial for them to reach statistical significance.

It is of interest that whilst most of the organisms in the control group were those usually associated with urinary tract infection, the bacteria in the infected urine from the treatment group of patients were all streptococci. It would appear that the mixture of antibiotics used for the irrigation was effective in eradicating all organisms other than the streptococci. Polybactrin Soluble GU has a broad spectrum of activity, the neomycin and polymyxin being active against Gram-negative bacteria, and the bacitracin acts in particular against Gram-positive organisms. It is possible that this growth of streptococci in the treatment group is due to the antibiotic solution rendering the patients more susceptible to resistant organisms, but it is more likely that whilst the concentration of neomycin and polymyxin in the half-strength used in this trial remained adequate, the concentration of bacitracin had become too low to be effective. It is interesting to speculate that if the quantity of bacitracin in the mixture were to be increased, the new antibiotic combination could be effective in completely preventing post-cystoscopy urinary tract infection. A further study using this new mixture in the irrigating fluid for cystoscopy is commencing.

Irrigation of the bladder during cystoscopy with Polybactrin Soluble GU appears to be a safe procedure and no harmful effects were observed. No patient presented with symptoms of, or returned a urine sample suggestive of, a reaction against the antibiotic solution.

Whilst it might be expected that destruction of part of the bladder mucosa by diathermy would render the bladder more liable to infection, this was not the case. The incidence of infection was the same whether per-urethral diathermy was performed or not.

It is concluded that the incidence of urinary tract infection after cystoscopy may be higher than is usually quoted.

The regime of bladder irrigation used in the study reduced the incidence of post-cystoscopy urinary infection, but this failed to reach statistical significance. A better spectrum antibiotic mixture might significantly reduce the incidence of post-cystoscopy urinary infection. Per-urethral diathermy of bladder tumours does not render the bladder more liable to infection.

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President: W. L. F. Utley (Christchurch)
Honorary Secretary: P. O. Maher (Sydney)
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Management of Non-seminomatous Tumours

By R. F. Gittes, J. P. Richie and M. B. Garnick
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Radiation therapy has been abandoned in favour of combined surgery and chemotherapy in this disease. Cases without detectable metastases (Stage I) and those with early node involvement (elevated markers) but no bulky disease on CAT scan are treated with retroperitoneal node dissection, with care to protect the ejaculatory reflex by sparing the sympathetic ganglia and hypogastric plexus on one side. Only cases with detected distant metastases (Stage III) or "bulky" nodes over 2 cm ("advanced" Stage II) detected by CAT scan, or positive markers after retroperitoneal node dissection receive chemotherapy in the form of 4 cycles of vinblastine (0.2 mg/kg/days 1,2), bleomycin (30 μ weekly) and cis-platinum (20 mg/m^2/days 1-5). They then have "evaluative" surgical resection of residual retroperitoneal masses. Later they receive added cycles of adriamycin (50 mg/m^2) and cyclophosphamide (500 mg/m^2), 5 cycles if the excised tumour consisted only of mature teratoma or fibrosis and 10 cycles if "active" or immature cells were found.

About 90% of such advanced cases have been found free of disease at a median follow-up of 2 years. Since retroperitoneal node dissection alone is a proven curative procedure for 80% of early Stage II cases, the later "rescue" of the surgical failures by chemotherapy offers an overall better than 95% cure rate for Stages I to II, while sparing the vast majority from the rigors of chemotherapy and from the long-term limitations of radiotherapy.

Non-seminomatous Testicular Tumours—The British Experience

By J. P. Blandy
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The question whether radiotherapy or lymph node dissection is better for non-seminomatous testicular tumours is still actively debated after 20 years. During this period there has been a steady improvement in the technique and results of either form of treatment, but a direct comparison has been made difficult by constant improvement and change in methods of detecting retroperitoneal metastases by lymphography and CAT scanning, their monitoring by αFP and βHCG markers necessitating repeated redefinition of the stage of the disease. Frequent changes in histological nomenclature have further confused the issue, and the discovery of tumour markers by immunoperoxidase techniques in seminoma once more raises the whole question of the validity of such pathological classification. A recent careful review of the evidence suggests that there was little to choose between the results of radiation or node dissection until about 4 years ago, when many North American centres reported far superior results—at least in embryonal carcinoma—after node dissection. This superiority could largely be explained by the different criteria used for staging, but in any event the original area of controversy has been largely rendered irrelevant by the impressive achievements of chemotherapy developed very largely in the same centres where the concomitant perfection of the technique of node dissection had permitted accurate and exact pathological staging.

It is suggested that the time has come to address our attention to the new questions which have been raised, *e.g.* how far does radiotherapy prevent subsequent chemotherapy being safely used and what purpose is served by removing tissue which proves on histological examination to be merely fibrous tissue or mature teratoma?

Chemotherapy of Non-seminomatous Testis Tumours—Its Value and Its Problems

By B. M. Colls
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Disseminated malignant teratoma of the testis has always offered clinicians a severe therapeutic challenge. Surgery and radiotherapy can hope to cure only early disease. The development of effective chemotherapy in association with retroperitoneal node dissection has revolutionised the outlook and promises to displace radiotherapy. Monitoring of serum alpha-fetoprotein and beta-subunit HCG tumour markers, which are found in some 80% of cases, has also assisted.

Twenty years ago the results of chemotherapy produced 7% long-term survivors; now, using the regime described by Einhorn and Donohue (1977), 74% of patients with disseminated tumours had a complete remission. In addition, survivors of this regime may be cured, since most relapses occur within 2 years of treatment.

Combined cyclical chemotherapy regimes are not without their problems; they are labour-intensive and produce adverse effects which, unless handled skilfully, are unacceptable. The Einhorn agents are: cis-platinum, which causes considerable nausea and vomiting, alopecia, renal damage and ototoxicity; bleomycin, which causes fever, rigors and interstitial pulmonary damage; vinblastine, which is a potent marrow toxin. The Christchurch experience with the Einhorn regime includes 18 evaluable cases. In all 18 cases an objective improvement was obtained and 13 entered complete remission. Adverse reactions were frequent, but acceptable.

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Surgical Aspects in the Management of Testis Tumours

By Warren Johnson

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Eighteen patients have undergone retroperitoneal lymph node dissection for testis tumour over a 10-year period. Twelve were staging procedures and 6 were for apparent or real failure of irradiation or cytotoxic therapy. Fourteen patients had embryonal cell carcinoma, 2 teratocarcinoma, one teratoma and one interstitial cell tumour.

Nine patients had malignant tissue removed and 7 of these, as well as all 9 who had negative node dissections, are alive and well without obvious evidence of disease with an average follow-up of over 4 years. All patients who had positive nodes have received either irradiation or cytotoxic therapy post-operatively except for 2 where resistant residual tissue was removed.

Lymphography has been used extensively and although the histological correlation is poor so far, it is still advocated, especially when combined with skinny needle aspiration cytology of abnormal nodes.

Ejaculatory impotence has occurred in all patients but there has been little demand for the use of stored semen. No surprise variations in histology between primary and metastatic disease have been encountered. Heroic debulking surgery should be embarked on with caution and without haste, since even clinically palpable masses after cytotoxic therapy may have histological pictures without certainty of active malignancy.

Dyssynergia of the External Sphincter

By R. F. Gittes

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In patients with spinal cord injury, inappropriate increases of external sphincter tone in response to the contractions of the spastic or unstable detrusor muscle of the bladder account for the hypertrophic trabeculation and the ineffective emptying of the bladder. Dyssynergia of the sphincter zone was found, to some degree, in all of 83 patients with spinal cord injury, the higher the lesion the more severe the dyssynergia. There is no effective pharmacological treatment at present. Therapeutic options are limited. Paraplegics with an unstable bladder are treated with transurethral external sphincterotomy at the 12 o'clock position to produce total incontinence and then use external condom drainage. Quadriplegics usually require bladder neck resection in addition to sphincterotomy as their pressure studies show a high gradient across the bladder neck in addition to external sphincter dyssynergia.

The Significance of Bladder Speed in Urodynamics

By R. J. Millard

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A measurable parameter of detrusor function independent of urethral resistance can be obtained by the calculation of the maximum possible flow rate that could be achieved by the bladder were it to void under the notional circumstances of zero outflow resistance. From this mathematical analysis of the relationship between detrusor voiding pressure and urinary flow rate has emerged the concept of bladder "speed" as a quantifiable measure of detrusor contractility. Two hundred and fifty urodynamic assessments have been scrutinised and bladder speed calculated. The results in 50 normal men and 50 normal women showed a normal frequency distribution curve in both sexes. There appeared to be no demonstrable change in bladder speed with age. By contrast, obstruction to the bladder outlet caused a reduction in bladder speed an, by implication, in bladder contractility. The relief of outflow obstruction by prostatectomy or bladder neck incision was followed in the majority of cases by an increase in bladder speed and an associated improvement in urological symptoms and urinary flow rate. When the speed remained low the flow rate was poor and the patient dissatisfied. There was a strongly positive correlation between the effect of operation on bladder speed and the clinical and subjective assessment of the results of surgery.

The results of this analysis are relevant to the clinical urologist presented with a dissatisfied patient after an apparently adequate prostatectomy or bladder neck incision. By bearing in mind the concept of bladder speed, such patients with possible persistent diminution in bladder contractility may be directed for urodynamic assessment before being subjected to further operative procedures. Surgery is reserved only for those with demonstrable residual obstruction.

Evaluation of the Factors Affecting Urinary Flow Rates

By V. R. Marshall, Rosemary L. Ryall and G. Sinclair
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A major clinical problem in the assessment of patients with urinary symptoms is the measurement and validity of flow rates from those complaining of frequency. These patients are usually able to pass small volumes only and the value of flow rates in association with these volumes has, in the past, been generally regarded as dubious. This study examined the relationship between urinary flow rates and voided volume, particularly in the range 0 to 200 ml. The results from this study indicated that urinary flow rates reflect the voiding pressures and that flows resulting from small bladder volumes are reliable indicators of bladder function as shown by excellent correlations obtained between flow and volume at volumes less than 150 ml. The flow volume curve was separated into 2 components and it seemed that the initial slope of the flow volume curve may be of more value than the peak flow in discriminating between normal people and those with voiding difficulties. The peak flow was represented by the flattened or plateau part of the flow versus volume curve. It was also found from this study that over filling the bladder, as can occur during cystometry, may result in low flows with flat patterns which could be erroneously interpreted as obstructive.

An Evaluation of Urinary Symptoms in the Female

By E. P. Arnold, A. Hope and N. MacEachern
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A significant proportion of the failures of routine operations for urinary incontinence in the female have been shown to have detrusor instability.

It is impracticable and costly for all female patients with disorders of micturition to undergo the sophisticated programme of urodynamic studies before surgery. It is therefore important to recognise the possibility of the presence of detrusor instability from the history, both in planning treatment and for assessing results. In this analysis, 207 women attending the Urodynamic Clinic at Dunedin Public Hospital were reviewed.

In the first group of patients who complained of incontinence, but denied poor stream or burning and frequency attacks, it was found that there was a high incidence of detrusor instability in those where urgency, urge incontinence, frequency and nocturia were among the symptoms. If stress incontinence was the sole symptom, 90% had stable bladder function.

The second group of patients with attacks of burning and frequency among their other urinary symptoms were difficult to assess. Most had stable function but many had mixed pictures. Fifty-nine of 68 had an inflammatory cause such as urethro-trigonitis, chronic cystitis or interstitial cystitis.

Urodynamic prediction in the third group of patients with poor stream among their other symptoms was again unreliable in that 26 of 35 had had previous gynaecological surgery, but only 23 of 35 had objective evidence of outlet obstruction.

It was concluded that if the history includes a poor stream, full urodynamic study is indicated. If attacks of burning and frequency are featured, a cystoscopy is indicated to exclude or treat any inflammatory cause. However, if stress incontinence is uncomplicated by other symptoms it is fair to assume that the bladder function is stable, whereas if urge incontinence, frequency and nocturia are features, detrusor instability is likely and this requires appropriate confirmation and evaluation by urodynamic testing before considering therapy.

Outflow Obstruction in Adult Males

By Christine M. Evans, M. Mohan Rao, G. Sinclair and V. R. Marshall
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The diagnosis of outflow obstruction due to the prostate has been made traditionally on history, clinical examination and the intravenous urogram, with some reliance being placed upon cystoscopic examination. This study was carried out to establish the value of urodynamic assessment in this situation to see how it correlated with clinical assessment. It was found that the presence of trabeculation correlated with obstruction as defined by urodynamic parameters, but residual urine did not. When comparing clinical assessment with urodynamic assessment, there was overall agreement in 62% of instances. We consider that there was minor disagreement in 22% and in nearly all of these instances the clinical assessment was equivocal and would have required periodic review of the patient. It was in this group that the urodynamic studies did provide useful information about the management of the patient and also enabled the detection of atonic bladders, which would have been missed on clinical assessment. There was major disagreement in only 6% of instances, and this is where the clinical assessment would have advocated operation, but this was avoided by the addition of urodynamic studies. However, it did not appear that urodynamic assessment was infallible and, as a result, we believe it should be used only in conjunction with, and not as a substitute for clinical assessment.

Endoscopic Management of Post-traumatic Urethral Strictures

By J. P. Mitchell

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The commonest and most serious complications of lower urinary tract trauma are stricture, incontinence and impotence. The incidence of these is difficult to assess because:

(*a*) at least 10 years' follow-up is needed to be sure no stricture will form,

(*b*) the degree of incontinence can be only subjective,

(*c*) impotence is almost universal until accident compensation has been settled.

Incontinence may be neurogenic but it is most likely to be due to direct damage to the external sphincter and posterior urethra.

Stricture of the posterior urethra treated by urethroplasty is successful in 70% of cases but re-stenosis, hairballs and diverticula have occurred and the operation is difficult in children and adolescents. The advent of the direct vision telescope with fibre illumination has made endoscopic urethrotomy feasible. The author described his own urethrotome which was first used in 1968. The technique under visual control is simple and was particularly effective in 13 failed cases of posterior urethroplasty and also in difficult strictures. The author's 10 FG children's urethrotome has been used effectively in the management of 5 cases of traumatic stricture of the posterior urethra in children. A silicone catheter (or fine silicone tube in children) is essential for 7 to 10 days following the endoscopic urethrotomy and insertion of the catheter or tube can be facilitated by the use of a special splint (Storz) sheath which can be left in the urethra after removal of the endoscope as a guide for the catheter.

The Management of Urethral Strictures

By J. P. Blandy

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Developments in urethroplasty have meant that today there is a wide range of different operative procedures from which the surgeon may choose. However, by far the safest of all methods of management of the urethral stricture remains intermittent, gentle, skilled and regular dilatation. When dilatation is difficult, internal urethrotomy often makes it easier and needed less often. However, the outcome of internal urethrotomy, with or without the visual urethrotome, remains unpredictable, giving worthwhile improvement in about half of the patients but nevertheless well worth trying. There remain many patients in whom dilatations are needed too often, are too painful, traumatic, or even frankly impossible. Here some type of urethroplasty is needed. For meatal strictures the simple n-flap meatoplasty is easy and certain. For anterior strictures the Leadbetter-Yaxley-Orandi urethroplasty is ideal, and similar viable islands of skin, on their pedicle of dartos, can be used to patch strictures of almost any length and in almost any part of the urethra. When multiple fistulae and abscesses complicate the picture, the old 2-stage scrotal flap inlay is used. Occasionally, hairs give rise to stones and there may be re-stenosis following some 7% of all types of urethroplasty. Hence it is important that every care should be taken to prevent the formation of strictures so bad that they cannot be easily managed by simpler methods, and for this reason it becomes specially important that in the management of fractured pelvis with disrupted membranous urethra, every care is taken to reduce the dislocation of the soft parts by reduction of the displacement of the bony pelvis—if necessary by external fixation.

Acute Trauma to the Lower Urinary Tract

By J. P. Mitchell

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The majority of lower urinary tract injuries are consequent upon road traffic accidents. In 2 series, one of 88 cases in adults and the other of 24 cases in children, more than 75% of the cases were seen within a few hours of injury. Surgical attention to the lower urinary tract is not considered a matter of urgency, as urine extravasation is not a serious complication within the first 24 h of injury.

A diagnosis of ruptured urethra can be made on clinical signs of blood at the external meatus, inability to pass urine and a bladder which becomes palpable in due course.

Less than 10% of posterior urethral ruptures were total transections and therefore it seems that every care should be taken to avoid inflicting further damage by the use of the diagnostic catheter. This may introduce infection or cause further iatrogenic trauma, while at the same time providing little helpful diagnostic evidence in the majority of patients. The incidence of lower urinary tract trauma in all cases of fractured pelvis in the Bristol series was 4.7%. This is the lowest recorded association and may be due to conservative avoidance of surgical trauma. In the cases of total transection (less than 10%), immediate catheter splintage was advised, but the remainder required only suprapubic drainage. Diagnosis of total transection was made when the bladder and prostate were found floating high in the abdomen at the time of formal suprapubic approach. Rectal examination in such patients can be misleading.

In those patients treated by suprapubic drainage, endoscopy of the urethra was performed at least 3 weeks after the injury and in two-thirds of those patients it was possible to see the way through and negotiate the inevitable S-shaped distortion of the urethra. In one-third however, open retropubic exploration was required.

Adenocarcinoma in Urinary Diversion to the Colon: Experimental Studies

By R. F. Gittes and M. Crissey

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Adenocarcinoma of the colon arising at the junction of the urinary and colonic epithelia occurs in over 5% of patients with long-term ureterosigmoidostomy. A model of this localised tumour has been achieved in rats, such tumour arising in 12 of 17 rats surviving 8 to 12 months after diversion of the urinary bladder to empty into the rectum. The question of whether such tumours might arise clinically in colon loops was addressed also. Rats with a colostomy diverting the faecal stream proximal to their urinary-colonic junction never developed junctional tumours (0/31). It is apparent that isolated intestinal conduits are not especially susceptible to urine-born carcinogens, but that the admixture of faeces and urine somehow activates carcinogens which are short-lived and act upon the junctional intestinal epithelium. The model offers the opportunity for experimental definition of this condition and perhaps prevention of this localised form of tumour.

End-stage Reflux Nephropathy

By R. R. Bailey

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Gross vesicoureteric reflux is the essential pathogenic factor in the aetiology of the small, scarred kidney of non-obstructive, chronic pyelonephritis (reflux nephropathy). Eighteen (12.5%) of 144 patients entering a dialysis-transplant programme had end-stage reflux nephropathy.

There were 6 male (mean age 20.2 years) and 12 female patients (mean 18.7 years). Of the 6 males only one had a documented urinary tract infection and this was asymptomatic and detected at the time of presentation. Five of the 12 women had suffered a proven urinary tract infection. Fourteen of the patients had hypertension, which in 10 was observed for the first time at presentation. A 12-year-old boy and a 9-year-old girl presented with malignant hypertension. Eight of the 12 women presented during a pregnancy. In 6 of these the clinical syndrome was one of severe or atypical "toxaemia of pregnancy". Five of the 6 men and 6 of the 12 women had severe renal failure at the time of presentation. All patients had proteinuria (mean 2.5 g/24 h; range 0.9 to 7.2 g) but none had the nephrotic syndrome. The mean age of commencement on regular dialysis treatment was 24.5 years for the male and 28.7 years for the female patients. Six of the 18 patients had HLA-B12 tissue type. Fourteen patients have received a renal transplant.

Reflux nephropathy is a significant cause of end-stage chronic renal failure which could be potentially eliminated by detecting and surgically correcting gross vesicoureteric reflux either in infants or in young children.

Some Observations on the Effect of Reflux on the Adult Kidney

By E. P. Arnold, J. D. Billings and W. L. Wright

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Bipolar coarse scarring, typical of reflux nephropathy, can occur in the previously normal adult kidney when faced with ureteric reflux and infection.

Others have observed renal damage when the ureteric orifice has been damaged, for example at resection of bladder tumours, so as to allow reflux, but only in the presence of infection.

We have observed damage typical of reflux nephropathy in high spinal injury patients with a grossly uninhibited bladder and detrusor sphincter dyssynergia in the presence of marked vesicoureteric reflux.

Reflux after ureteroileal diversion is a common event under the abnormal circumstances of a radiologist's conduitogram. The contents of the conduit are often infected but damage to the previously normal kidney occurs in only 10 to 30%. The damage may be post-obstructive atrophy, but is sometimes typical of reflux nephropathy and several examples were presented.

The pressure of reflux may be important. It has been shown that intrarenal reflux or pyelotubular backflow can occur at pelvic pressures exceeding 100 to 130 cm water. Such pressures have been observed in the spinal injury patient with reflux and uninhibited bladder contractions with detrusor sphincter dyssynergia, but also were observed in the current study when deliberately occluding the stoma of an ileal conduit in 6 out of 10 cases.

It therefore appears likely that in the normal adult kidney, just as in the developing and infant kidney, vesicoureteric reflux with intrarenal reflux, plus urinary infection, may lead to reflux nephropathy. It may well be that the pressure of reflux is an important initiating factor. Once infection has occurred the pressure at which intrarenal reflux arises may well be much lower than in the uninfected state.

Results of Ureteric Reimplantation in Severely Scarred Kidneys

By C. U. McRae

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Most kidneys in children with severe reflux grow at a normal rate following reimplantation and control of infection. A few severely damaged kidneys do not grow after reimplantation and continue to deteriorate. The cause of the progressive deterioration is unknown but may be due to continuing infection, reflux, hypertension or a glomerulopathy.

In 14 children with a severely scarred kidney followed from 8 to 20 years, 11 kidneys grew at a normal rate but 3 continued to deteriorate. Three patients had persistent proteinuria and one hypertension.

It is concluded that the majority of severely scarred kidneys still have the potential for the normal remaining renal tissue to grow but a few will continue to deteriorate in spite of apparently adequate treatment.

Management of Ureteric Reflux with Observations on Renal Growth Following Ureteric Reimplantation

By C. Dale Vermillion

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One hundred and one children with ureteric reflux were followed for at least 2 years. This included 201 ureters of which 160 had demonstrated reflux. Reimplantation was carried out on 63 ureters with a 96% success rate. In those ureters handled conservatively, 100% of ureters with less than Grade III reflux stopped spontaneously if the patient was under 2 years of age and in 92% if the patient was under the age of 4. However, no patient over the age of 4 with Grade IIB reflux stopped refluxing spontaneously and 2 of these ultimately developed renal scarring, suggesting the need for ureteric reimplantation in this group.

The renal growth rate following ureteric reimplanta-was variable. It was either greater than or equal to expected rates if no renal scarring was initially present. In those children with bilateral ureteric reflux and only unilateral scarring, the growth rate was considerably greater in the non-scarred kidney. In patients with bilateral reflux and bilateral scarring, all kidneys had expected growth rates except in 3 patients with 6 badly scarred kidneys who demonstrated significantly slower growth rates than expected, suggesting that irreparable damage had occurred prior to reimplantation.

Incidence of Vesicoureteric Reflux in Infants with Sterile Urine

By G. D. Abbott, B. Taylor and T. M. J. Maling

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The incidence of vesicoureteric reflux in children without a previous history of documented urinary tract infection is thought to be very low, though there is some variance in the reports in the literature.

In Christchurch all infants and children admitted to hospital have a voided specimen of urine cultured to detect bacteriuria. The high contamination rate and low confidence limit of a single bag specimen of urine as an indicator of urinary tract infection in infancy has been well documented. If infants had greater than 100×10^6 organisms/l, a bladder puncture was performed to confirm or deny the presence of true bacteriuria. In this study 50 infants of less than 1 year of age, who were in hospital for a variety of reasons but not thought to have urinary tract infection, had greater than 100×10^6 organisms/l on a bag urine and therefore had a bladder puncture. At the time of bladder puncture urine was aspirated for culture and 30% Urovision was instilled into the bladder by gravity and a single X-ray was taken as the infant voided. Five of 50 infants had asymptomatic bacteriuria documented and 2 of these had vesicoureteric reflux. Of the remaining 45 infants with sterile urine, 4 had vesicoureteric reflux (11%), 3 were graded as moderate and 1 gross. The infant with gross reflux had a further micturating cystogram 6 weeks later and the reflux had disappeared.

In this study, therefore, in infants without clinical or bacteriological evidence of urinary tract infection, the incidence of vesicoureteric reflux was 11%.

Congenital Megacalices

By R. F. Gittes

Peter Bent Brigham Hospital, Boston, USA

Radiological recognition of the non-obstructive nature of the large calices of congenital megacalices avoids unnecessary surgery for what is often incorrectly termed "intrarenal hydronephrosis". There is a common association of such megacalices with a similarly non-obstructive segmental widening of the distal ureter—the pelvic megaloureter which may also be subjected to unnecessary surgery on the incorrect assumption that it has caused the caliectasis. Scintigrams with dimercaptosuccinic acid, acetazolamide, penicillamine, or any other tubule-specific isotope will demonstrate the normality of the renal cortex surrounding the large calices. If needed, antegrade pressure-flow studies can resolve the question of whether there is ureteric obstruction.

Hypothermia in Transurethral Resection of the Prostate*

By J. K. Walton and R. E. Rawstron

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Ninety-three patients having transurethral resection of the prostate for benign hyperplasia were studied over an 18-month period. A control group of 44 cases was resected using irrigant at room temperature. The trial group of 49 cases was resected using irrigant cooled to 2°C. Pre-operative blood loss and resected prostatic weight were measured.

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The mean prostatic weights of the 2 groups were comparable, the control group being 18.61 g and the cold group being 20.04 g. Other variables which could influence blood loss, such as patient age and mean operating time, were comparable between the 2 groups.

The mean blood loss in the control group was 289.57 ml, and the mean blood loss in the cold group was 240.29 ml. The smaller blood loss in the cold group amounts to a 17% reduction in blood loss. This reduction in blood loss was not statistically significant in the 93 cases studied ($0.5>P>0.3$). It was concluded that the use of cold irrigating solution in transurethral resection of the prostate does not significantly reduce blood loss.

Oestrogen and Androgen Receptors in Benign Prostatic Hyperplasia and Carcinoma of the Prostate

By W. D. Tilley, D. D. Keightley and V. R. Marshall

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The measurement of hormone receptors in human breast cancer has now been clearly established as an important predictor of the likely response of these tumours to hormonal manipulation. In attempting to extend this approach to prostatic cancer, cytoplasmic oestrogen, progesterone and androgen receptors were measured in 133 men undergoing transurethral resection of the prostate. The incidence of these receptors for oestrogen, progesterone and androgen was 16, 33 and 28% respectively. We also found that there was a significant increase in the incidence of both oestrogen and progesterone receptors with the age of the patient. This correlation may be of significance in relation to the known increase in the incidence of malignancy with age. The incidence of androgen receptors in the cytoplasm was lower than we would have anticipated in view of the fact that the prostate is an androgen target organ. To examine the possibility that some of the receptors in the cytoplasm were being masked by endogenous androgen or, alternatively, are localised in the nucleus, an exchange assay, as well as a nuclear androgen receptor assay, was developed; using these techniques, the incidence of androgen receptors in the cytoplasm increased from 28 to 58% and all of the nuclear extracts examined were receptor positive. Thus it would appear that receptor patterns are more complicated in benign prostatic tissue than in breast tissue, and that simple cytoplasmic assays may not be sufficient to allow receptor incidence to be used clinically.

Experience with a Urological Account Card/Data Retrieval System

By R. D. Wines and H. M. Learoyd

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There is a wealth of clinical material contained in the notes of patients seen in private practice, but mostly the information is tedious to recover and not in a form available for easy recall.

Data retrieval using the Kalamazoo fact finder system was described. A urological punch card was designed on the reverse side of the patient's account card. The system allows recall of selected information and access to notes of patients with rare conditions. The system is always up-to-date and requires the minimum of medical and secretarial time. This system has been successfully used for 3 years.

Results of Prostatectomy after Cerebrovascular Accident

By S. K. Lum and V. R. Marshall

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Cerebrovascular accidents and outflow obstruction caused by the prostate are both common and increase in frequency with advancing age. This study has examined the results that were obtained in 34 men who had undergone prostatectomy following a cerebrovascular accident. (All but 3 patients had transurethral resections of the prostate.) It was evident that there was an increased mortality rate when compared with other series looking at the results of prostatectomy—11% died within 3 months of the operation, and 24% died within one year. None of these deaths was directly related to the prostatic surgery. The incidence of urinary symptoms following the procedures was high, and 50% were judged to have had an unsatisfactory result with regard to urinary control. The patient age, the neurological deficit, and the presence of chronic retention, all tended to adversely affect the outcome of prostatectomy. However, the major influence on the outcome was the site of the cerebrovascular accident—if the non-dominant hemisphere was involved, the patient generally had a poor outcome. Finally, if the operation was performed within a year of the cerebrovascular accident, then again one could anticipate a poor result.

Radiation-induced Bladder Cancer

By D. R. H. Kennedy

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A series of patients irradiated for cervical cancer between 1959 and 1969 and followed for 10 to 20 years is reviewed. Eight hundred and seventy-three patients were treated and of these 331 survived 10 years or more. In this latter group 4 patients developed a primary bladder carcinoma after a latent period varying between 11 and 16 years.

The annual incidence rate of bladder cancer in the female population is 4.9/100,000. The exposed population at risk is 4905 person years. Therefore the expected number of cases is 0.240. The observed number is 4 and is 17 times greater than expected. This figure is statistically significant ($P<0.001$).

Haematuria following radiation treatment for carcinoma of the cervix is usually due to vesical telangiectasia. Since it may occasionally be due to a bladder tumour, all such cases should be fully investigated and cystoscopy should be repeated if bleeding recurs.

The Significance of Microscopic Haematuria Found on Health Testing

By John Wheelahan

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From 7389 patients undergoing automated multiphasic health testing, 475 patients were selected by the finding of microscopic haematuria without bacteriuria or pyuria. Haematuria was detected by both microscopy and dipstick testing; the criteria for inclusion were a red blood cell count of >20 cells per ml or an equivalent level on dipstick testing.

A follow-up study of the investigations and diagnoses was made. Fifty-six patients had clinical diagnoses made of urinary tract disease but only 33 of these were new diagnoses. There was only one patient with urologic disease requiring surgery, a symptomless staghorn calculus.

It was concluded the yield of previously unknown urologic disease was too small to justify the cost of the investigations performed. The problems of accurately detecting micro-haematuria and defining a normal range and the large number with transient micro-haematuria, make it an unsuitable bio-medical test on its own on which to base clinical decisions.

Follow-up investigation cannot be recommended in younger patients unless there is proteinuria, urinary symptoms or, in some cases, known urinary tract disease. In patients over the age of 50 the risk of neoplastic urinary tract disease is small, but further study is needed to determine if micro-haematuria has any value as a screening test for neoplastic disease.

Scrotal Gangrene

By H. W. Gowland

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It is almost 100 years since Fournier described the condition that was to bear his name. He emphasised the explosive onset, rapid progression to gangrene and lack of apparent cause. Many of the cases described subsequently have had a definite underlying cause, but there are some in which this is not evident. Developments in microbiology have helped to elucidate the problem. The introduction of antibiotic therapy has varied the clinical course immensely. Bacterial synergism is the common factor in a number of severe soft tissue infections involving mainly the perineum and adjacent areas. It is suggested that these synergisms are variants of a common theme.

Stone Disease: The Value of Metabolic Studies

By Rosemary L. Ryall, Christine M. Evans, V. R. Marshall and G. Sinclair

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The incidence of metabolic abnormalities and the value of stone analysis in the management of renal stones were studied in a group of 323 patients derived from a teaching hospital and a private practice source. It was of interest to note that the patients seen in private practice were, in general, older than those attending the teaching hospital and that the total numbers of individuals from higher and lower socio-economic groups were roughly equal.

Hyperparathyroidism was found to be extremely rare (1 case).

Important discrepancies were observed between the 2 sources of patients with respect to hyperuricosuria, with 55% of those from private practice having raised 24-h uric acid excretion, but only 8% of those from the hospital group. It appeared that the major cause of this difference was the fact that normality in each group was defined by widely disparate values, highlighting the need to establish reliable normal ranges for a given community. Normal values for 24-h uric acid excretion were far higher than those reported in the United Kingdom.

In examining the value of stone analysis, it seemed that careful analysis of radio-opaque stones only was necessary to establish the presence of urate. In these cases analysis should be quantitative to distinguish between stones consisting principally of uric acid as opposed to those composed mainly of calcium.

Congenital Polyps of the Prostatic Urethra

By M. R. Rajaratnam

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This is a rare benign congenital condition that occurs predominantly in infants and children. It is a solid epithelialised polyp that arises on or in the vicinity of the verumontanum. About 90% of patients present clinically with difficulty of micturition. Other symptoms are haematuria, symptoms related to infection and renal impairment.

Diagnosis is made on micturating cystourethrography, which shows a rounded filling defect in the bulbar or prostatic urethra. At urethroscopy the polyp is seen to arise either from the verumontanum or at a site adjacent to it. The larger polyps have a long stalk and are seen to prolapse through the bladder neck into the bladder. The smaller polyps are removed endoscopically by diathermy excision at the neck. The larger polyps are removed through a cystotomy incision. At follow-up the polyps that are adequately removed show no evidence of recurrence.

Histological examination in the majority reveals that these polyps are composed of a loose fibrous connective tissue core covered by transitional epithelium. In some the epithelium is replaced by hyperplastic squamous cells but with no keratinisation. The stroma may also contain smooth muscle, glandular elements and nerve tissue.

To date 45 cases have been reported in the world literature, establishing this condition as a definite pathological entity. Various terms have been used to describe this lesion. The most appropriate of these is congenital polyp of the prostatic urethra.

"Bench" Surgery of the Kidney in Renal Carcinoma

By R. F. Gittes

Peter Bent Brigham Hospital, Harvard Medical School, Boston, USA

Among 20 personal cases of surgery for tumour in a solitary kidney, 6 cases were complex enough (multiple or centrally located tumours) to require removal of the kidney to a platform adjacent to the operative wound, thus avoiding division of the ureter. This "bench" permitted cold arterial perfusion, leisurely tumour excision with confirmation of clear margins by frozen section, and accurate reconstruction of the vessels and collecting system. One case had bench surgery twice, 3 years apart, because of a new tumour arising in the cortex of the renal remnant. Of the 7 cases treated, one 74-year-old diabetic died with retroperitoneal sepsis, a mortality rate of 14%. Temporary post-operative haemodialysis was required in 3 cases. A solitary lung metastasis appeared in one case at 3 years; it was surgically removed and the patient appears tumour-free 4 years later. With 1 to 8 years of follow-up, all 5 patients have no evidence of renal failure and they are apparently free of tumour.

Disruption of the Pelviureteric Junction During Pyelolithotomy

By H. Story

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Disruption or avulsion of the pelviureteric junction probably occurs more commonly than reports in the literature would suggest. It is likely to occur when a stone has been present in an intrarenal pelvis for a long time. Anatomical and pathological features combine to permit easy disruption by a normally safe technique. Repair by suture may be difficult or even impossible due to friability of tissues. If the patient at risk is recognised, the complication might be avoided by meticulous care and better than adequate exposure.

In the case presented the pelviureteric junction disrupted without obvious cause and suture repair was impossible. In reconstitution of the pelviureteric junction the spatulated ureter was held in apposition to the renal pelvis by being sutured to a splinting catheter which itself was sutured to the renal capsule. Nephrostomy drainage was provided. The splint and nephrostomy were left in place for 4 weeks. A good anatomical and functional result was obtained as shown by intravenous urography at 2 years and renal scan at 3 years.

Sexual Rehabilitation Programme at the Otar Spinal Unit, Auckland

By A. J. Duke

Auckland, New Zealand

Following any severe illness or injury involving permanent disability, a person initially needs total care and reverts to a child-like state of dependency. Rehabilitation means helping the person to regain control over life, to become adult-like again, often with very major adjustments to be made. Sexuality, involving the whole personality as male or female, with the roles that society expects, is much more than sexual or genital function and is unaltered despite limitations in possible expression. Health means the ability to exercise options and part of rehabilitation is to allow the person to be aware of all available options during convalescence.

Society in general, including medical and nursing staff as well as partners and relatives, tend to equate disability with asexuality. All of these groups need to look at their attitudes and to help the patient come to terms with the reality of any loss of function and to increase the knowledge of all possibilities and options available for satisfying sexual expression.

The Otara Spinal Unit has between 40 and 50 new patients each year. There is a 3:1 male:female ratio and the majority are in the 20 to 30 year age group. As part of the genitourinary assessment the sexual possibilities are fully discussed with the patient and partner and appropriate counselling provided. In the main rehabilitation programme regular sessions are held to allow staff, patients and partners to be involved in group discussion. Information and films are provided. Long-term follow-up includes sexual assessment as well as a review of bladder function. Counselling is provided as required. This subject can fall neatly within the urological area and become truly genitourinary.

Is a Microsurgical Technique for the Re-anastomosis of the Divided Vas Necessary?

By D. Urquhart-Hay

Wellington Hospital, Wellington, New Zealand

It is accepted that microsurgical re-anastomosis of the vas following vasectomy will result in a pregnancy rate as high as 65% with a "sperm return rate" of about 95%. However, the technique is one requiring considerable expertise gained only after long practice in the animal laboratory, and it also requires expensive and sophisticated equipment. Comparable results can be obtained using a simple and conventional technique in which fine sutures, splintage and low power magnification (×3.5) are used, making it ideally suitable for the surgeon untrained in microsurgical techniques.

The essential points in the technique include minimal mobilisation of each vas end, the insertion of a very fine nylon splint removed within 6 to 8 days, and the insertion of 4 7/0 non-absorbable sutures through the seromuscular layer only, with the aid of low power magnification. The patient is immobilised for the first 48 h and encouraged to have coitus within 10 to 14 days of the procedure. Prednisone 40 mg daily for a period of 6 weeks may help in the prevention of postoperative fibrosis at the anastomosis site.

Such a technique has been used in 50 men undergoing vasovasostomy following vasectomy, resulting in a pregnancy rate of 52% and the reappearance of sperms within the semen in 84% of the patients.

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Case Reports

Ruptured Ureter in Pregnancy—a Unique Case?

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Renal and ureteric stones present uncommonly as colic during pregnancy. The reported incidence varies between 0.05 and 0.35% (Harris and Dunnihoo, 1967) and the incidence in each trimester is not significantly different. Several authors have, however, reported more cases in primigravidae (Zerner, 1975).

In the majority of reported cases the stone has passed spontaneously. However, there are many reports in the literature of removal of stones either by ureteric instrumentation or ureterolithotomy. The occasional patient has required nephrectomy but in these cases there has been a long history of renal disease.

We present a patient with ureteric rupture secondary to impacted calculus who presented in the third trimester of her first pregnancy. We could not find any previously reported similar cases.

It is also of interest that this patient had no preceding documented history of urinary tract infection or other urological problems.

Case Report

A 27-year-old primigravida was referred at 30 weeks' gestation with a 6-week history of left-sided loin pain, the onset of which had been acute and severe with radiation to the left groin and associated sweating and vomiting. A course of amoxycillin had been prescribed by the General Practitioner but had failed to relieve the symptoms and she was, therefore, admitted by the obstetricians, when a diagnosis of pyelonephritis was made. At that time the urine cultures grew *Proteus mirabilis* sensitive to amoxycillin.

She remained unwell and pyrexial with a swinging temperature and marked loin tenderness despite continued antibiotic therapy. A mass gradually became apparent in the left loin. At this time urine cultures were negative but the patient had a neutrophil leucocytosis of 23.5×10^9/l. Antibiotics were continued but the leucocytosis persisted and urine cultures began to grow *Escherichia coli*.

A provisional diagnosis of perinephric abscess was made. Ultrasound examination showed an anechoic mass below the left kidney and apparently separate from it. Despite the continuing pregnancy it was then considered mandatory to clarify the diagnosis by performing a limited excretion urogram.

A preliminary plain film showed an opacity 1.5 × 0.75 cm adjacent to the left transverse process of L1. The left kidney was laterally displaced by a rounded mass below it. A film 20 min after contrast showed dilatation of both pelvicaliceal systems consistent with advanced pregnancy but no filling of the left ureter occurred (Fig. 1). The opacity was seen just distal to the pelviureteric junction. A delayed oblique film (with lead shielding of the fetus) showed contrast within the mass which was, therefore, a urinoma (Fig. 2). A diagnosis was thus made of ruptured ureter due to impacted stone with retroperitoneal extravasation of urine. On the basis of this information surgery was planned.

The left kidney was explored through a loin incision. The urinoma was evacuated and the stone, which was

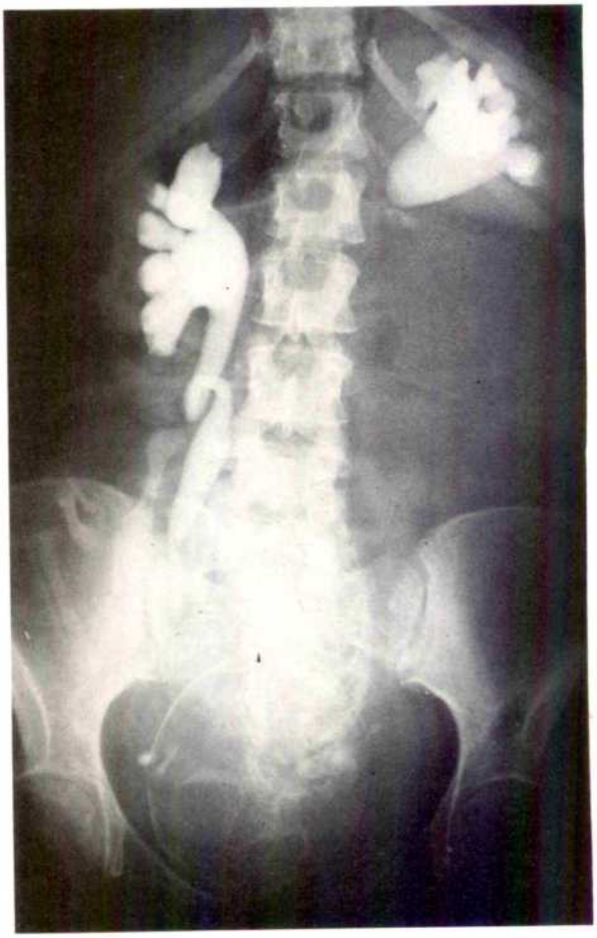

Fig. 1

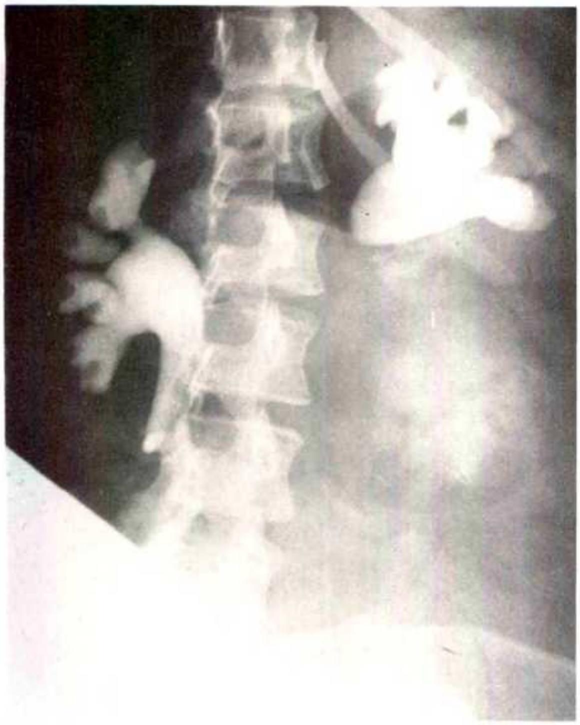

Fig. 2

lying free, was removed. No attempt was made to identify the distal ureter. A nephrostomy tube was inserted.

The post-operative course was uneventful and the pregnancy proceeded to a forceps-assisted delivery at 37 weeks of a normal 2.02 kg female infant. A postpartum tubogram demonstrated continuing extravasation with no drainage to the bladder. A repair procedure was then undertaken through the original incision. The distal ureter was found embedded in a mass of granulation tissue with scattered urine-filled cavities. The site of rupture was identified and excised and healthy ureter was sutured to the renal pelvis with an indwelling ureteric splint. A tubogram performed 10 days postoperatively demonstrated no extravasation, so the nephrostomy tube was removed and 2 days later the ureteric splint was taken out. Urine drainage from the wound ceased within a week and a midstream urine specimen was sterile. The patient was discharged home where she continued to remain well. A follow-up urogram at 3 months showed normal anatomy with no loss of cortical thickness.

Discussion

The stone had probably formed within a calix and with the physiological pelvicaliceal dilatation of pregnancy became dislodged, to impact in the proximal ureter. Its size and shape prevented its passage, causing pressure necrosis and subsequent rupture (Trapnell, 1969).

The initial presentation was that of classical ureteric colic. But for the pregnancy an excretion urogram would undoubtedly have been ordered at that time and the diagnosis made clear. Intervention then would have modified the course of events. Natural reluctance to expose the fetus to radiation delayed correct diagnosis. As a consequence surgical management was complicated and the patient's morbidity was increased and prolonged into the puerperium.

A limited excretion urogram (usually 2 films only) often involves less fetal irradiation than films of pelvis and fetus in late pregnancy, yet there is little hesitation in carrying out these examinations, which are still frequently requested. Similarly, no such caution prevails in the radiological investigation of neonates, especially the premature where the risks must be similar (Carmichael and Berry, 1976). In the third trimester the risk is not of fetal malformation but of possible oncogenesis in childhood (Russell and Russell, 1952).

Had the diagnosis been made at the time of presentation it is probable that a one-stage ureterolithotomy would have sufficed. The delay and rupture necessitated a 2-stage procedure (Trapnell, 1969) with additional risk to the pregnancy and patient of continuing sepsis following initial drainage. In this case the definitive procedure had to be postponed until the puerperium, when the uterus was no longer compressing the ureter.

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Chronic Inflammation of the Ureter with Urothelial Ingrowth Simulating Inverted Papilloma

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Case Report

A 63-year-old man was admitted with haematuria and nocturia. One year previously he had had right renal colic. Apart from a slight elevation of blood urea (7.14 mmol/l) and serum uric acid (0.49 mmol/l) the laboratory data were normal. Physical examination was normal except for moderate benign enlargement of the prostate. An excretion urogram revealed a non-functioning right kidney and a radiolucent staghorn stone within the left renal pelvis.

A right retrograde pyelogram demonstrated complete obstruction of the ureter 7 cm from the ureterovesical orifice. The bladder mucosa appeared normal.

The right ureter was explored through a midline incision. Below the iliac vessels the ureter was thickened and adherent, while above the vessels it was dilated. When the thickened part of the ureter was opened the lumen was found to be obliterated and the mucosa oedematous; no stones were found. A frozen section suggested the diagnosis of inverted papilloma (Fig.) and a right nephroureterectomy was carried out. The kidney was small and hydronephrotic and 2 regional lymph nodes were histologically negative. The patient made a good recovery and 2 months later underwent a left pyelolithotomy.

Serial histological sections of the ureteric wall failed to show as many epithelial buds as in the frozen section. The ureteric wall was thickened but occupied mainly by fibrous tissue with many capillary vessels and lymphocytes. Transitional cell nests were found only immediately under the urothelium.

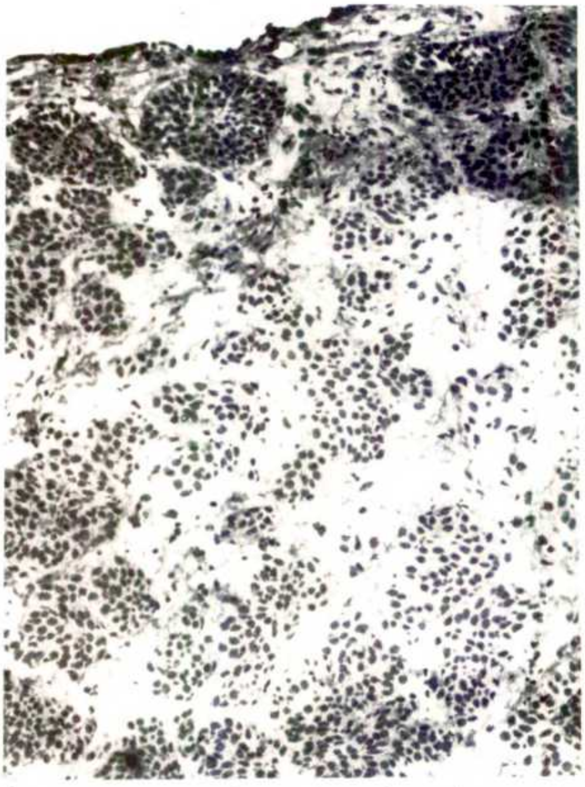

Fig. Frozen section of operative specimen demonstrating rich urothelial buds ingrowth underneath normal mucosa (H and E ×125).

Comment

Von Brunn cell nests and cystic lesions are responses by the urothelium to chronic irritation and it is difficult to distinguish them from inverted papillomas, which are often present in adjacent areas (De Meester *et al.*, 1975).

Inverted papillomas have been found near bladder tumours (Melicow, 1974) and have been considered to have a role in the development of carcinoma. Hence inverted papillomas are now regarded as benign tumours and although most are found in the bladders of elderly males, a few have been found in the renal pelvis (Cameron and Lupton, 1976).

Urothelial ingrowth is seldom described in the ureter and while considered pre-cancerous by some, others regard it as merely a bizarre form of hyperplasia.

In the present case we suspect that a uric acid stone impacted at the level of the iliac vessels could have caused chronic inflammation and proliferative changes in the mucosa and led to complete obstruction.

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Bilateral Xanthogranulomatous Pyelonephritis

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Xanthogranulomatous pyelonephritis is a rare condition that may mimic renal carcinoma or abscess. This case, whilst illustrating many typical features, is thought to be only the third reported with bilateral renal involvement.

Case Report

A 37-year-old man presented with a month's history of anorexia, weight loss, malaise and vague abdominal pain related to micturition. There was no relevant past medical history. On examination he was dehydrated and pyrexial, with a normal blood pressure. A large mass was palpable in the right flank and urine testing revealed heavy proteinuria and haematuria. Initial blood tests showed a haemoglobin of 10 g/dl (MCV/MCH normal), a neutrophil leucocytosis of 12×10^9/l and an ESR of 115 mm/h. His urea was grossly elevated at 72.6 mmol/l, serum sodium 122 mmol/l, potassium 4.5 mmol/l and bicarbonate 18 mmol/l. A significant growth of *E. coli* was cultured from the urine and blood.

He was rehydrated and given antibiotics and a small urine output was maintained, but his mental state deteriorated and peritoneal dialysis was commenced. The patient rapidly improved and renal function stabilised (serum urea at 10 mmol/l, creatinine 250 μmol/l).

Plain abdominal films suggested that both kidneys were enlarged, and this was confirmed by high dose intravenous urography (IVU). Renal angiography showed an 18 cm right kidney and a 15 cm left. The appearances on both sides were identical with a normal vessel pattern and poorly defined renal outline. The nephrogram looked "moth eaten" and the renal vein opacified poorly (Fig.). Percutaneous biopsy of the right kidney showed the histological picture of xanthogranulomatous pyelonephritis.

Comment

Xanthogranulomatous pyelonephritis usually presents as a unilaterally enlarged, non-functioning kidney. Partial involvement or a shrunken kidney are occasional findings. Whilst some reports have shown suspected abnormalities on IVU in the opposite kidney, only 2 definite cases of bilateral involvement have been demonstrated. The first was by Rossi *et al.* (1968), where both kidneys were almost completely involved (angiography and autopsy), and the second by Vandendris *et al.* (1976), where localised disease was present in both kidneys (angiography, biopsy, one kidney). The present case demonstrates complete involvement of both kidneys with some renal function preserved.

Acknowledgements

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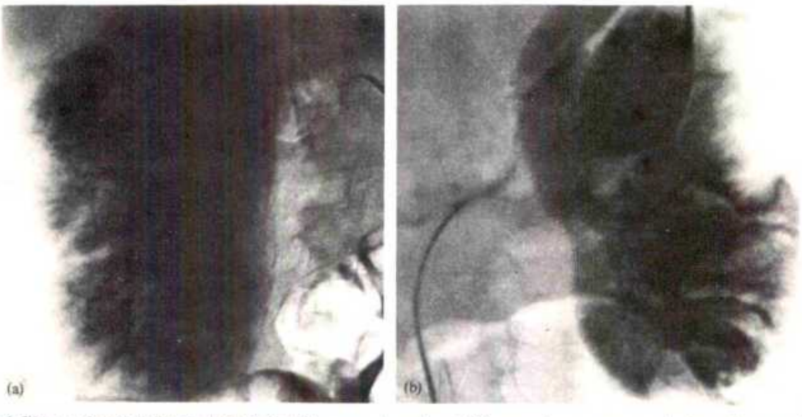

Fig. Subtracted films of (a) right and (b) left kidneys, showing diffuse enlargement and "moth-eaten" nephrogram.

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Ruptured Renal Carcinoma in a Child

C. M. BOOTH, *Urology Registrar, St Paul's Hospital, London WC2H 9RE*

Renal carcinoma is very rare in children. This report describes an unusual presentation.

Case Report

A 10-year-old girl presented with vomiting and abdominal pain 24 h after a light blow in the abdomen. There was tenderness and guarding over a mass in the left hypochondrium. A sample of urine was normal.

A diagnosis of a ruptured spleen was made, but at laparotomy a large retroperitoneal haematoma was evident. This appeared to be a ruptured, apparently pyonephrotic kidney with blood and yellow caseous material issuing from a tear in the anterior surface of the middle of the kidney. The centre of the kidney was destroyed. A nephrectomy was performed from which the child rapidly recovered.

Histology

The kidney contained a 4.5 cm diameter cyst with blood and friable yellow tissue spilling through an anterior tear (Fig.). This was an encapsulated cystadenocarcinoma consisting of solid masses of uniform cells with areas of papillary formation.

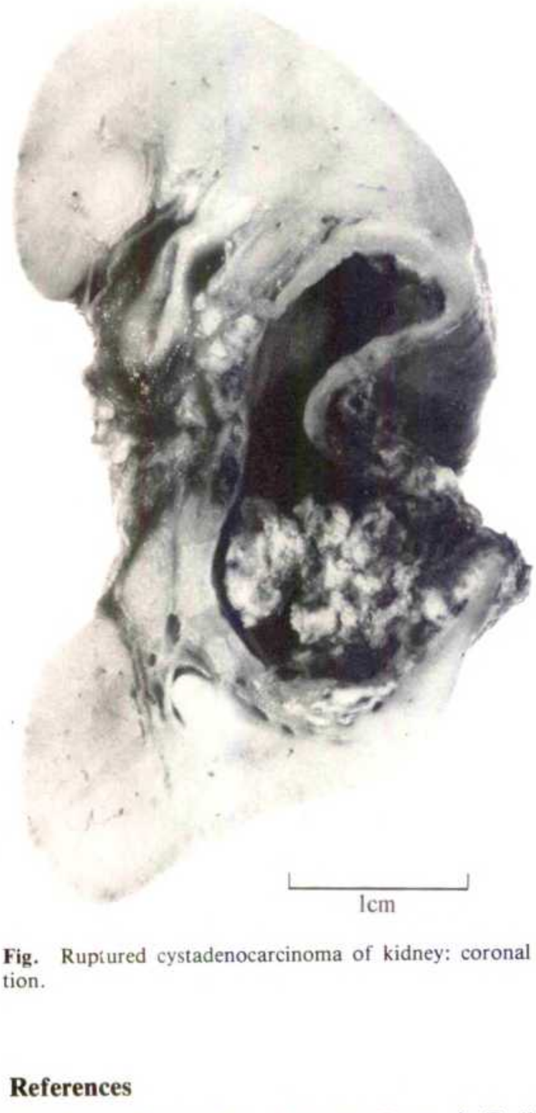

Fig. Ruptured cystadenocarcinoma of kidney: coronal section.

Comment

About 120 verifiable cases of renal carcinoma have been reported in children, the youngest being a 3-month-old baby (Kobayashi *et al.*, 1970). The tumour occurs worldwide with an equal sex ratio. Most children present with non-specific complaints and less than 10% with loin pain, haematuria and a mass. The tumours behave like their adult counterparts and the overall survival rate is 50% (Castellanos *et al.*, 1974).

There have been 4 reports of ruptured renal cell carcinoma in children; 3 followed trivial trauma (Manson *et al.*, 1970) and one occurred spontaneously. One was a cystadenocarcinoma. All have survived following nephrectomy.

Acknowledgements

I wish to thank Mr J. A. S. Dickson, Dr N. E. France, Dr K. M. Cameron and Miss J. Brinnand for their help.

References

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Manson, A. D., Soule, E. H., Mills, S. D. and Deweerd, J. H. (1970). Hypernephroma in childhood. *Journal of Urology,* **103**, 336-340.

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0007-1331/81/02650083$01.00

Acute Small Bowel Obstruction 20 Years after Reimplantation of the Ureter

D. J. HAY *(University of Manchester School of Medicine), Hope Hospital, Salford*

A case of intestinal obstruction is presented where, on laparotomy, a loop of small bowel was found to be obstructed by a previously reimplanted right ureter. The implications are discussed.

Case Report

A 69-year-old woman was admitted with a 12-h history of colicky abdominal pain, vomiting and constipation. She was a chronic bronchitic on treatment with Ventolin tablets and a Ventolin inhaler and also suffered from hypertension which was well controlled. Some 20 years previously she had had a hysterectomy for fibroids and one week later a further exploration was performed and the right ureter was reimplanted into the bladder.

On examination she was in pain but her general condition was good. The cardiovascular system was normal. An examination of the chest revealed scattered crepitations and some expiratory rhonchi. The abdomen was soft but distended and there was some tenderness over the right kidney and in the right iliac fossa. No masses were palpable. The bowel sounds were mildly obstructive. A rectal examination revealed no abnormality. X-rays of the abdomen in the erect position showed a dilated small bowel loop with fluid levels (Fig.) Laparotomy was performed through a right paramedian incision. There were adhesions in the peritoneal cavity, but the cause of the obstruction was a band across the cavity of the pelvis which had trapped and strangulated a loop of small bowel. The band was divided and the obstruction relieved. The use of hot packs improved the condition of the small bowel and resection was unnecessary. The divided band was a firm, fibrous cord extending from the pelvic brim just to the right of the midline to the fundus of the bladder and on further examination this was found to be the right ureter which had been lying across the peritoneal cavity. The ureter proximal to the pelvic brim was dilated but at the pelvic brim it narrowed down into the fibrous cord; as this was obviously unsuitable for reanastomosis it was excised and the remnant attached to the bladder was tied off.

The proximal ureter on the right side was markedly tortuous and was mobilised sufficiently to allow its reimplantation into the bladder, which was mobilised and hitched to the psoas. A ureteric catheter was threaded through the anastomosis into the bladder and then out through the anterior abdominal wall. The bladder was drained by a Foley catheter.

The patient's post-operative progress was uneventful and the ureteric catheter was removed on the fifth day after operation. The Foley catheter was removed 7 days post-operatively.

Comment

Although a detailed review of the literature has failed to reveal any previously reported case of intestinal obstruction caused by a divided ureter, this rare case serves as a further illustration of the necessity to take great care to obliterate any potential defects in the peritoneum which could give rise to internal herniae.

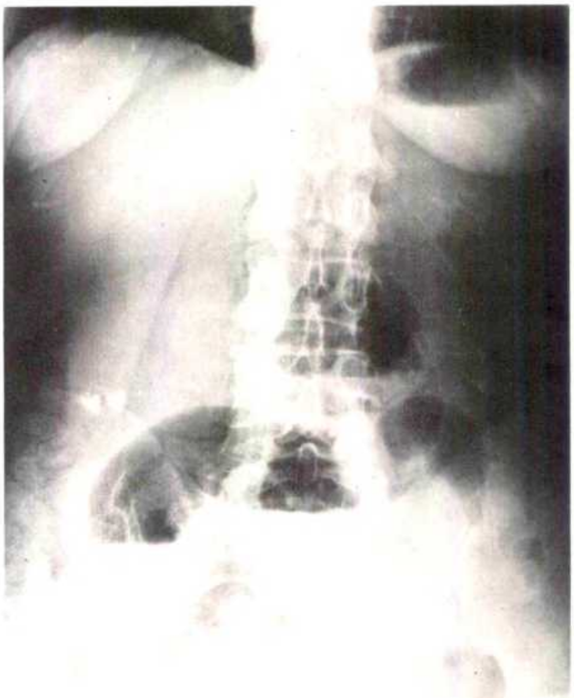

Fig. Abdominal X-ray.

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Points of Technique

A Transurethral Biopsy Punch for the Prostate Gland

A. E. KULATILAKE and D. F. EVANS, *Urological Unit, Department of Surgery, Queen's Medical Centre, University Hospital, Nottingham NG7 2UH*

A large proportion of surgery of the prostate gland is performed transurethrally using modern endoscopic devices. Resection of prostatic tissue is usually effected with a "hot" electric cautery wire-loop and only a small number of urologists use the "cold" punch resectoscope.

In our studies in prostatic cancer we need undamaged resected tissue samples. Thus a "hot" cutting loop is undesirable because of cellular damage caused by the heat of the loop. There is increasing evidence that various studies, including electron microscopy, tissue androgen and polyamine concentrations, are affected by the heat generated in these loops.

We describe a biopsy punch knife which has been developed to be interchangeable with the standard loop of the resectoscope.

The Biopsy Punch

A standard 27 FG resectoscope loop was cut off and replaced with a tubular cutter manufactured from stainless steel. A thin sharp metal cutting loop, using a short length of blade manufactured by Gillette for their Techmatic razor, was moulded into the tubular steel segment. This very thin, sharp blade could be replaced when necessary (Fig. 1). The blade was set at an angle to the cutter in order to obtain a slicing action when the working element was drawn forward. Thus solid tissue cylinders approximately 3 × 2 cm can be obtained with ease (Fig. 2).

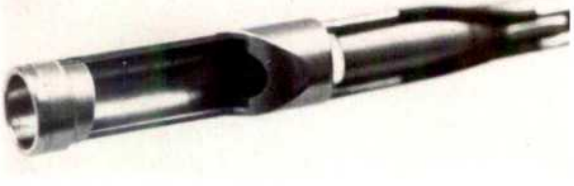

Fig. 1

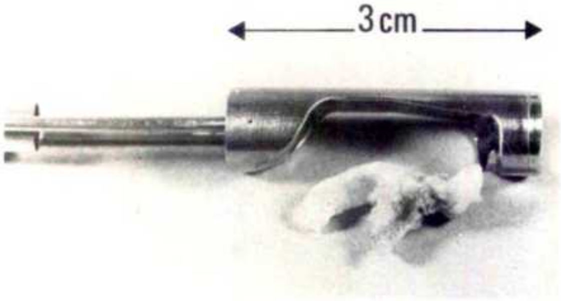

Fig. 2

Using a 0° telescope, a core of tissue can be biopsied easily under direct vision. Approximately 4 to 6 passes with the blade provide approximately 5 g of tissue, which is normally sufficient for most investigative measurements. After sufficient tissue has been removed, the biopsy punch is replaced by the resectoscope loop and any further procedure carried out as necessary.

Acknowledgements

We would like to thank Mr M. Taylor, of the University of Nottingham Medical School Faculty Workshop, for spending many hours making and modifying the prototype blades, and Mr Barker, of Gillette Industries, for supplying the replaceable blades.

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Notices

British Association of Urological Surgeons

President: W. K. Yeates, MD, MS, FRCS

Annual Meeting: London, 8-10 July 1981

Further information from: J. L. Williams, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2 3PN.

First Meeting. Urological Days of Necker

Paris, France. 12-14 March 1981.

The topics are:

(1) Tumours of calices, renal pelvis and ureter.
(2) Ureteropelvic junction obstructive anomalies.

The mornings of 12 and 13 March will be devoted to televised operations. The afternoons of these 2 days and the morning of 14 March will be devoted to communications. Each speaker will have 30 minutes at his disposal and the lectures will be published as monographs by Masson.

Further information from: Secrétariat des Journées Urologiques de Necker, Clinique Urologique, Hôpital Necker, 149 Rue de Sèvres, 75015 Paris, France.

The Urological Society of Australasia. Annual Scientific Meeting

Sydney, Australia. 22-27 March 1981.

Further particulars from: P. O. Maher, Hon. Secretary, 10 Wybalena Road, Hunters Hill, New South Wales 2110, Australia.

Bladder Cancer Symposium

Huddersfield. 2-3 April 1981

The main topics under discussion will be industrial bladder cancer and chemotherapy both in superficial and advanced bladder malignancy.

Further particulars from: R. W. Glashan, Department of Urology, The Royal Infirmary, Huddersfield HD3 3EA.

Edinburgh Urological Festival

Edinburgh. 31 August-2 September 1981

Part of this meeting will be devoted to original papers and their discussion, preference being given to those submitted on investigative and research topics; the other part will be a post-graduate course by invited speakers. The meeting is restricted to 80 participants. The closing date for submission of abstracts is 30 June 1981.

Further particulars from: Urological Festival Secretary, Department of Surgery, University Medical School, Teviot Place, Edinburgh EH8 9AG.

Second Congress of the International Society of Urologic Endoscopy

Bristol. 9-11 September 1981.

Those wishing to join the Society should contact the Honorary Secretary, Dr Jorge Morera, Federico Lacroze 2154, (1426) Buenos Aires, Argentina.

Those interested in attending the meeting should contact Miss Sarah Storie-Pugh, Conference Services Ltd, 3 Bute Street, London SW7 3EY.

The Urological Society of Australasia. Annual Scientific Meeting

Canberra, Australia. 29 March-1 April 1982

Further particulars from: P. O. Maher, Hon. Secretary, 10 Wybalena Road, Hunters Hill, New South Wales 2110, Australia.

Fifth Congress of the European Association of Urology

Vienna, Austria. 12-15 May 1982

Further particulars from: Prof. Dr S. Rummelhardt, c/o Vienna Medical Academy for Postgraduate Education, Alser Strasse 4, A-1090 Vienna, Austria. Telephone: (0222) 42 71 65. Cables: MEDACAD Wien.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

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Mr T. J. Millin, MA, MCh, Dubl, FRCSI, FRCS, FACS

Terence John Millin died at the age of 77, on 3 July 1980 at his home in Kilcoole, Co. Wicklow.

He was born in St Helen's Bay, Co. Down and educated at St Andrew's College, and then Trinity College, Dublin, where, as a medical student, he captured nearly every available prize and won an international cap for rugby before qualifying in 1928.

He obtained the FRCS Ireland, in 1928, FRCS England, in 1930 and in 1932 obtained an MA and MCh at Trinity.

He was an assistant surgeon in Sir Patrick Dun's Hospital before he moved to London where he became associated with Canny Ryall of All Saints Hospital and specialised in urology. He became a consultant at the Royal Masonic Hospital, St Helier's Hospital, Carshalton, and Chelsea Hospital for Women and was also honorary consultant surgeon to Westminster Hospital.

He was already a very successful urological surgeon when, in 1945, he published his technique of retropubic prostatectomy in *The Lancet* and his subsequent book on retropubic surgery published in 1947 gave him an international reputation and surgeons were attracted from all over the world to watch him operate. He was a most accomplished and dexterous surgeon with that unique quality that made difficult operations look easy, and there were endless invitations for him to work abroad.

He travelled a lot not only to meetings but also as a visiting lecturer or professor and very frequently to operate on distinguished citizens in foreign countries. He continued to make a valuable contribution to urological literature, notably in relation to vesical cancer and the urological aspects of gynaecology.

He was President of the Surgical Section of the Royal Society of Medicine in 1948, won the St Peter's Medal in 1951, and was elected President of the British Urological Association in 1954. Foreign distinctions included an Honorary Fellowship of the American College of Surgeons and of the Royal Australian College of Surgeons, and he was awarded the Francis Emery Prize by the American Academy of Arts and Sciences in 1954. He delivered the first T. J. D. Lane Memorial Lecture in Dublin in 1971 and became the first Honorary Member of the Irish Society of Urology in 1975. He was greatly touched in 1978 when members of the Section of Urology of the Royal Society of Medicine travelled specially to Dublin to give him an honorary fellowship.

He returned to live in Ireland and finally retired from active surgery at a surprisingly early age to become an outstanding President of the Royal College of Surgeons in Ireland in 1963 and after he stepped down in 1966 he continued to serve on the Council of the College. His contribution here was recently recognised by the establishment of The Millin Lecture offered annually to young surgeons.

Terence Millin was very popular with his colleagues and this largely derived from his own simplicity and his apparent unconcern with his great reputation. He was especially kindly and helpful to aspiring surgeons. He had a casual manner which was quite deceptive, because he was a man of decisive action when he felt strongly about something.

He had a great sense of humour and delighted in telling jokes and was a brilliant after-dinner speaker. Many members of the British Urological Association will remember with joy his highly amusing speeches at Annual Dinners in the 1950s. His contribution to urology was almost exclusively in the practical field and this reflected his personality and his devotion to the clinical aspects of urology. He was one of the great figures of surgery in this century and he has an assured place in the history of urology.

J.D.O'F.

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Book Reviews

Clinical Nephrology. S. Papper. Second edition. Pp. ix + 633. Boston: Little, Brown and Co., 1978. Price £15.30, US $22.50.

This book has been written predominantly for the non-nephrologist. It provides a comprehensive and easily understood account of renal disease, including fluid and electrolyte disturbance, and there is a handbook section on test procedures and treatment of renal disease which will be a valuable reference for the general physician. The strong emphasis on clinical management of the patient with renal disease is a good feature.

Unfortunately this otherwise excellent account of renal disease suffers because the author is, in many sections of the book, rather verbose, making reading somewhat tedious. For this reason I suspect that general physicians are likely to be attracted towards other accounts of renal disease which, although less comprehensive, are more concise.

Principles and Management of Urologic Cancer. Edited by N. Javadpour. Pp. xi + 533. Baltimore: Williams and Wilkins, 1979. Price £36.85, US $54.95.

Aspects of urological tumours have been well catered for in several recent texts, but this book sets out to cover the whole subject for the practising urologist, oncologist and student. It certainly achieves its aims to be comprehensive and includes chapters on epidemiology, aetiology and immunology as well as treatment. It is detailed and most of these chapters are excellent reference sources. However, these details in the text, and also the wordy style, prevent easy reading and this book is more appropriate for those with a special interest in the subject.

It was a surprise to find "Renal Neoplasms" as the running head for the chapter on prostatic cancer. Presumably the 1978 revision of the TNM classification was too late for inclusion and this is disappointing. All of the contributors are American, so that British readers must not be surprised to see some of their differing points of view on management omitted. A useful reference book.

Manual of Urologic Surgery. Edited by R. H. Egdahl. (Comprehensive Manuals of Surgical Specialities. Edited by A. T. K. Cockett and K. Koshiba.) Pp. 284. Berlin, Heidelberg, New York: Springer-Verlag, 1979. Price DM 238.00, US $133.30.

This fully illustrated book will be a useful addition to departmental libraries in the United Kingdom. Operations such as radical prostatectomy and retroperitoneal node dissection, which are uncommon in this country, are well shown. The way in which the illustrations are numbered makes it a little awkward to follow the operative steps easily, but this is a minor criticism of an otherwise very comprehensive manual.

Renal Pathology. Postgraduate Pathology Series. E. M. Darmady and A. G. MacIver. Pp. xii + 548. London: Butterworths, 1980. Price £35.00.

In the Postgraduate Pathology Series edited by Sir Theo Crawford, the authors took up the challenge of covering the wide scope of kidney pathology in a rather concise text.

After 3 chapters on development, normal kidney and growth changes, the work embraces the different pathological lesions affecting this organ, from congenital lesions to neoplasia through metabolic, immunological, vascular lesions, etc. The last chapter is devoted to nephron microdissection, a fascinating but rarely used technique, and also to a useful summary of immunological tools in nephropathology.

The authors have not restricted themselves to gross and microscopic descriptions but have made enlightening incursions into clinical pictures, biochemical changes and sometimes into treatment rationales. A simplified classification at the beginning of each chapter would have been welcome, since nosology and nomenclature of kidney lesions are still far from clear-cut.

This work, which is written in a clear and precise style, will nevertheless prove very useful to those physicians, surgeons and pathologists who, although not concerned directly with kidney disease, wish to know more about this important subject.

A Patient's Guide to Dialysis and Transplantation. R. Gabriel. Pp. 128. Lancaster: MTP Press Ltd, 1980. Price £4.95.

It was an excellent idea for Dr Gabriel to write a guide for patients who have developed chronic renal failure and who require long-term treatment with dialysis and/or transplantation. The text is well set out with clear line drawings and the chapters cover most of the important subjects, providing answers to many of the questions that these patients ask.

Chapters on dialysis techniques and on kidney disease are rather detailed and will be more than most patients can absorb and understand, although they would be instructive to the interested and informed reader. Some topics are rather glossed over; for example, the psychological problems of adjusting to long-term treatment for the patient and his family really require more explanation and depth. Sexual difficulties are dealt with very cursorily, and yet this is a major—although often unexpressed—problem for many patients.

The chapter on social service support may be useful to some patients, but actually obtaining these benefits usually requires further expert help from a social worker. Again the advantages and disadvantages of home dialysis versus transplantation for the older patient require further explanation than can be given here, and it should be emphasised that the treatment policy may vary considerably between different renal units.

Despite these minor criticisms, this book fills a valuable place in the literature available to patients.

Radionuclides in Nephrology. Proceedings of the IVth International Symposium, Boston, 1978. Edited by N. K. Hollenberg and S. Lange. Pp. xvi + 280. Stuttgart/New York: Georg Thieme Verlag, 1980. Price DM 98.00.

The publication of conference proceedings is a standard bête noir of reviewers. This volume is a report of the proceedings of the 4th International Symposium on Radionuclides in Nephrology held in 1978.

There is little that is new or not published elsewhere, so that the main value of a volume such as this is that it collects together, into one easily accessible volume, a good deal of work that is otherwise scattered widely throughout the world literature, and it provides a useful summary of the current views of most of the leading workers in this field.

This is a useful volume and source of references to anyone concerned with the application of radioisotopes in nephrology. Its chief shortcoming is careless editing. A number of otherwise useful papers are difficult to understand because of their bad English. If a paper is worth publishing at all (and these papers are worthy of publication), it is the duty of editors to ensure that it is in language which is both grammatical and colloquial. The editors of this volume have failed in this task, and in so doing have been gravely discourteous both to their contributors and their readers. There are many examples of sloppy editing, of which page 227 is the prime example. To read both the text and the table it is necessary to hold the book in the conventional orientation, side on and upside down—is this a record? In summary, a useful volume spoilt by carelessness.

Radiology of the Urinary System, Volumes I and II. Edited by M. Elkin. Pp. 1286 + index. Boston: Little, Brown and Co., 1980. Price $55.00 each volume.

In the preface to this monumental work the author claims that it sums up his own personal experience in uroradiology. This experience proves to be profound, for with the exception of a few specialist chapters written by associates, Professor Elkin has personally contributed the bulk of the 1300 pages of this 2-volume text. The result is a masterly and comprehensive study of the scope of uroradiology, including the newer imaging methods.

In the initial chapters, techniques are studied in detail, as are the embryology and congenital abnormalities of the urinary tract. Most of the ensuing chapters are orientated towards either problems or pathology, the latter sections being devoted to such special areas as paediatrics, renal transplantation, computerised tomography, nuclear medicine and ultrasound.

Throughout both volumes the well annotated radiographs are supported where necessary by good line drawings. One cannot avoid being impressed by the way in which the author has complemented his radiological experience with much relevant background clinical and pathological detail. Radiology is thus placed firmly in the context of clinical practice.

Allowing for the fact that new imaging methods are undergoing continuous and rapid evolution, this work undoubtedly provides a good basic reference on the subject of uroradiology and therefore will be of value both to the clinician and to the radiologist.

Books Received

Advances in Nephrology. Volume 9. Edited by J. Hamburger, J. Crosnier, J.-P. Grünfeld and M. H. Maxwell. Pp. xix + 423. Chicago, London: Year Book Medical Publishers, 1980. Price £41.

Séminaires d'Uro-néphrologie, sixième série. Published under the direction of R. Küss and M. Legrain. Pp. viii + 190. Paris: Masson, 1980.

Membrane Physiology. Edited by T. E. Andreoli, J. F. Hoffman and D. D. Fanestil. (Reprint of Parts 1-3 of Physiology of Membrane Disorders, 1978.) Pp. xiii + 468. New York: Plenum Press, 1980. Price $19.95.

CURRENT UROLOGICAL LITERATURE: SELECT BIBLIOGRAPHY[1]

The List of Current Urological Literature is now arranged to correspond to the order in which the papers are published in the *Journal, i.e.* in anatomical order beginning with papers on the Adrenal.

A general section is included at the end.

ADRENAL

Effects of unilateral adrenalectomy on the ultrastructure of the remaining adrenal. (P. K. Ray.) *J. Kuwait Med. Assoc.* 1980, **14**, 61.

Morphologic features of the anencephalic adrenal gland in early pregnancy. (E. S. Gray and D. R. Abramovich.) *Am. J. Obstet. Gynecol.* 1980, **137**, 491.

Radiation diagnosis of adrenal pheochromocytoma and paraganglioma. (F. P. Khripta.) *Vopr. Onkol.* 1980, **26**, 85.

Leydig-like cells in the adrenals of a woman with ectopic ACTH syndrome. (E. Horvath *et al.*) *Hum. Pathol.* 1980, **11**, 284.

Evaluation for adrenal hypofunction. (S. Cunningham *et al.*) *Ir. J. Med. Sci.* 1980, **149**, 133.

The case of the adrenal mass. (W. B. Seaman.) *Hosp. Pract.* 1980, **15**, 137.

Preventing adrenal insufficiency during surgery. (R. L. Byyny.) *Postgrad. Med.* 1980, **67**, 219.

Complete remission of Cushings disease by total bilateral adrenalectomy and adrenal autotransplantation. (D. Barzilai *et al.*) *J. Clin. Endocrinol. Metab.* 1980, **50**, 853.

Inhibition of adrenal sterodiogenesis by danazol invivo. (R. J. Stillman *et al.*) *Fertil. Steril.* 1980, **33**, 401.

Adrenal androgen production in hyperprolactinemic states. (S. Belisle and J. Menard.) *Fertil. Steril.* 1980, **33**, 396.

Radiology of the adrenal gland. (F. Heuck *et al.*) [8 papers] *Radiologie*, 1980, **20**, 149.

Benign cystic dysplasia of adrenal glands in case of prune belly syndrome. (L. H. Honoré.) *J. Urol.* 1980, **123**, 562.

Surgery of the adrenal: result of 154 operations. (F. Kümmerle *et al.*) *Dtsch. Med. Wochenschr.* 1980, **105**, 679.

Microadenomatosis of the adrenal cortex and hypercorticism in pubertal age. (E. I. Marova *et al.*) *Sovet. Med.* 1980, No. 3, 15.

Ectopic adrenal tissue. A case report. (F. M. Draiby *et al.*) *Prensa Med. Argentina*, 1980, **67**, 35.

Ganglioneuroma arising in accessory adrenal gland. (G. M. Tertzakian and H. W. Herr.) *Urology*, 1980, **15**, 401.

Hypokalemic myopathy with serum enzyme elevations and failure of adrenal scintiscan in a patient with adrenal adenoma —case report. (A. A. Zaloznik and K. D. Mccowen.) *Milit. Med.* 1980, **145**, 186.

Computer tomography in the diagnosis of adrenal disease. (U. Mödder *et al.*) *Dtsch. Med. Wochenschr.* 1980, **105**, 478.

Adrenal gland haematoma in a new-born infant: diagnosis and follow-up ultrasonography. (J. L. Ferran *et al.*) *Ann. Pediatr.* 1980, **27**, 391.

Cis-platinum treatment of metastatic adrenal carcinoma. (M. H. N. Tattersall *et al.*) *Med. J. Aust.* 1980, **1**, 419.

Localization of aldosterone-producing tumours in primary aldosteronism by adrenal and renal vein catheterization. (J. O. Lund *et al.*) *Acta Med. Scand.* 1980, **207**, 345.

Coexistence of pituitary adrenocorticotropin-dependent Cushings syndrome with a solitary adrenal adenoma. (D. E. Schteingart and H. S. Tsao.) *J. Clin. Endocrinol. Metab.* 1980, **50**, 961.

Bilateral adrenal neuroblastoma. (S. A. Kramer *et al.*) *Cancer*, 1980, **45**, 2208.

Adrenal myelolipoma associated with Cushing's disease. (B. D. Bennett.) *Am. J. Clin. Pathol.* 1980, **73**, 443.

KIDNEY

General. Renal autotransplantation for recurrent renal colic. (C. A. Olsson and B. Idleson.) *J. Urol.* 1980, **123**, 467.

Chronic renal disease in childhood. (W. B. Macdonald.) *Aust. Paediatr. J.* 1980, **16**, 1.

Chronic renal disease in childhood—doubts, hopes and expectations. (R. Adler.) *Aust. Paediatr. J.* 1980, **16**, 47.

Parenchymatous kidney diseases. *Münch. Med. Wochenschr.* 1980, **122**, 732.

Use of immunofluorescence and electron microscopy in the diagnosis of renal disease. (A. R. Graham and R. B. Nagle.) *Ariz. Med.* 1980, **37**, 357.

Recent advances in the treatment of renal disease. (R. S. Brown and J. S. Stoff.) *Drug Ther.* 1980, **5**, 15.

Splenic compression of the left kidney simulating pathologic unilateral renal enlargement. (C. M. Sandler *et al.*) *J. Comput. Assist. Tomogr.* 1980, **4**, 248.

Morphological alterations in the kidneys due to carbon tetrachloride poisoning. (L. N. Zimina *et al.*) *Arkh. Patol.* 1980, **42**, 15.

Concrescent kidney. (P. Guembe *et al.*) *Rev. Clin. Esp.* 1980, **156**, 289.

The renal acidoses. (F. C. Rector and M. G. Cogan.) *Hosp. Pract.* 1980, **15**, 99.

Quantitative nephrotoxicity of gentamicin in nontoxic doses. (B. Trollfors *et al.*) *J. Infect. Dis.* 1980, **141**, 306.

Compensatory hyperplasia of the human kidney evaluated by angiography and a dye dilution technique. (J. Göthlin.) *Acta Radiol.* 1980, **21**, 43.

Nephronophthisis. (B. T. Steele *et al.*) *Am. J. Med.* 1980, **68**, 531.

Kidney disease therapy and the school. (M. Broyer.) *Arch. Fr. Pédiatr.* 1979, **36**, Suppl. 2, xxiv.

Compensatory renal hypertrophy (CRH). (B. Debre.) *Sem. Hop. Paris*, 1980, **56**, 1004.

The incidence of the renal venous collar in South African blacks. (B. Kramer and F. E. Grine.) *S. Afr. Med. J.* 1980, **57**, 875.

Renal mass in man with eosinophilic granuloma. (D. E. Crawford *et al.*) *Urology*, 1980, **15**, 520.

Renal lesion in Jeunes syndrome. (K. J. Shah.) *Br. J. Radiol.* 1980, **53**, 428.

Viruses and the kidneys. (R. G. Filimonova.) *Ter. Arkh.* 1980, **52**, 143.

Treatment of renal amyloidosis. *Lancet*, 1980, **1**, 1062.

The assessment of the renal capacity for acidification with arginine hydrochloride. (J. Garciapuig *et al.*) *Rev. Clin. Esp.* 1980, **156**, 393.

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[1] Titles in this list have been taken from those listed in *Current Contents: Clinical Practice* published by Institute for Scientific Information, Philadelphia.

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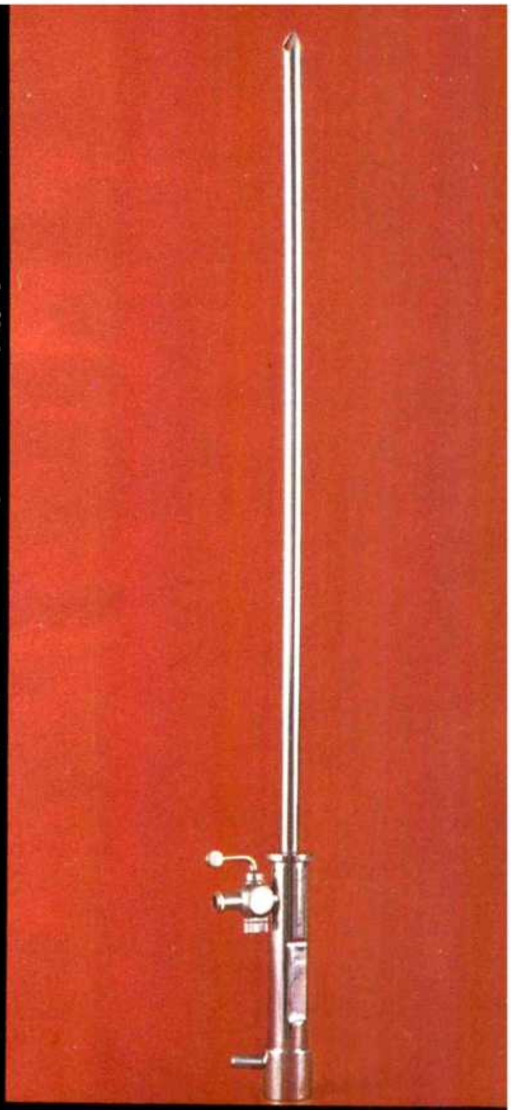
latest addition to the urological armamentarium

a new endoscopic urethral stricture dilator



1. View of the new endoscopic urethral dilator sheath. Fit in Forward Oblique (30°) or Direct Vision (0°) telescope inside and the endoscopic dilator is ready for use. The dilator is marked like an ureteric catheter for quick measurement of the distance of stricture. Water-inlet with stop cork is provided.
2. Close-up view of the triflanged tip of the dilator.

Dilation of the urethra is one of the most frequently done procedures both in the general surgical and urological set-ups. Dilation of the strictured urethra is usually done with metal dilators, sounds or bougies. Whichever dilator is used for dilation, the entire process is **totally a blind process. False passage** is the commonest complication, which adds insult to the already damaged urethra, with associated bleeding, infection and periurethral abscesses.

All the above problems can now be totally avoided by using the latest **endoscopic urethral stricture dilator,** designed and perfected by Dr. Shivadeo S. Bapat, of Pune, Maharashtra State, India. (Reference: Bapat S.S. A NEW ENDOSCOPIC DILATOR: Journal of Urology, 122: 30-34, —1979).

With the use of the above dilator complication of false passage and its associated sequelae can now be totally avoided, because the entire process of dilation of the strictured urethral segment is done completely under visual control.

This dilator can be satisfactorily used to dilate all varieties of strictures—short, long, tough, tortuous or multiple. Even those strictures with pre-existing false passages can be safely dilated. Patients presenting with acute retention of urine due to strictured urethra can be saved of an emergency suprapubic cystostomy by dilating the urethra with this dilator.

This dilator dilates the strictured segment to 18 Fr. (6 mm). Subsequent management of the strictured segment is, of course, left to the operating surgeon or the urologist. Further dilation of the strictured segment with standard bougies poses no problem due to the wide passage created by the endoscopic dilator. If the operator decides to perform internal urethrotomy, it can be safely carried out immediately.

This dilator is extremely easy to use. All you have to do is to fit in either a Forward Oblique (30°) or Direct Vision (0°) telescope within the dilator sheath. Then pass this dilator-cum-endoscope into the urethra after suitable anaesthesia and lubrication. The process of dilation with this endoscopic dilator is shown in the accompanying endoscopic colour photographs.

Important: Lateral telescopes (70° or 90°) that are used in cystoscopes **can not** be used with this endoscopic dilator.

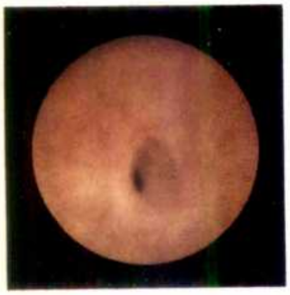


Fig. 1. A very tight stricture in uethra as seen through a standard panendoscopic sheath.

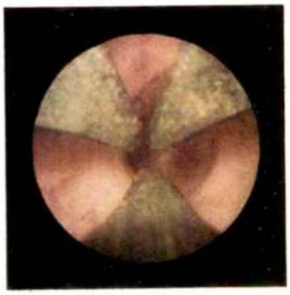


Fig. 2. Triflanged tip of the new endoscopic dilator seen in the urethra. The tight stricture is clearly visualised through the gap at the dilator tip.

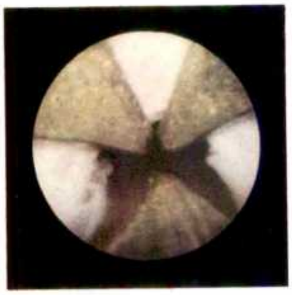


Fig. 3. The three tips of the triflanged dilator are engaged in the stricture and the dilator is advanced with steady and gentle pressure. Note the whitish fibres of the fibrous tissue being separated and the view of the proximal dilated urethra.

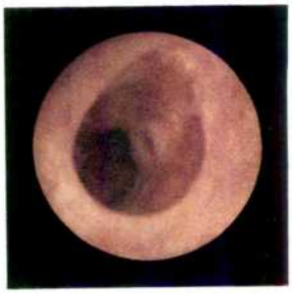


Fig. 4. View of the strictured segment after successful dilation by the new endoscopic urethral stricture dilator. This photograph has been taken through a standard panendoscopic sheath. Compare this with Fig.1.

Mail this Order Form to us.

Please send me the invoice with CIF value
of your new endoscopic urethral stricture dilator.
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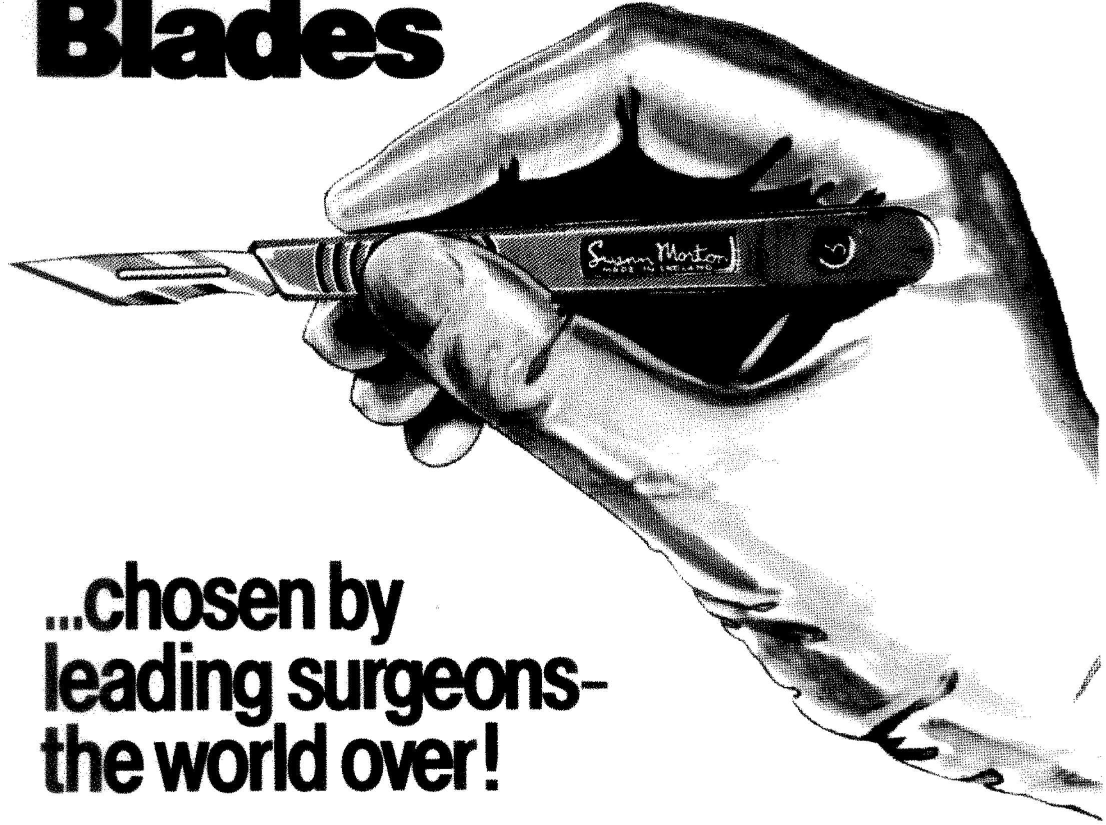

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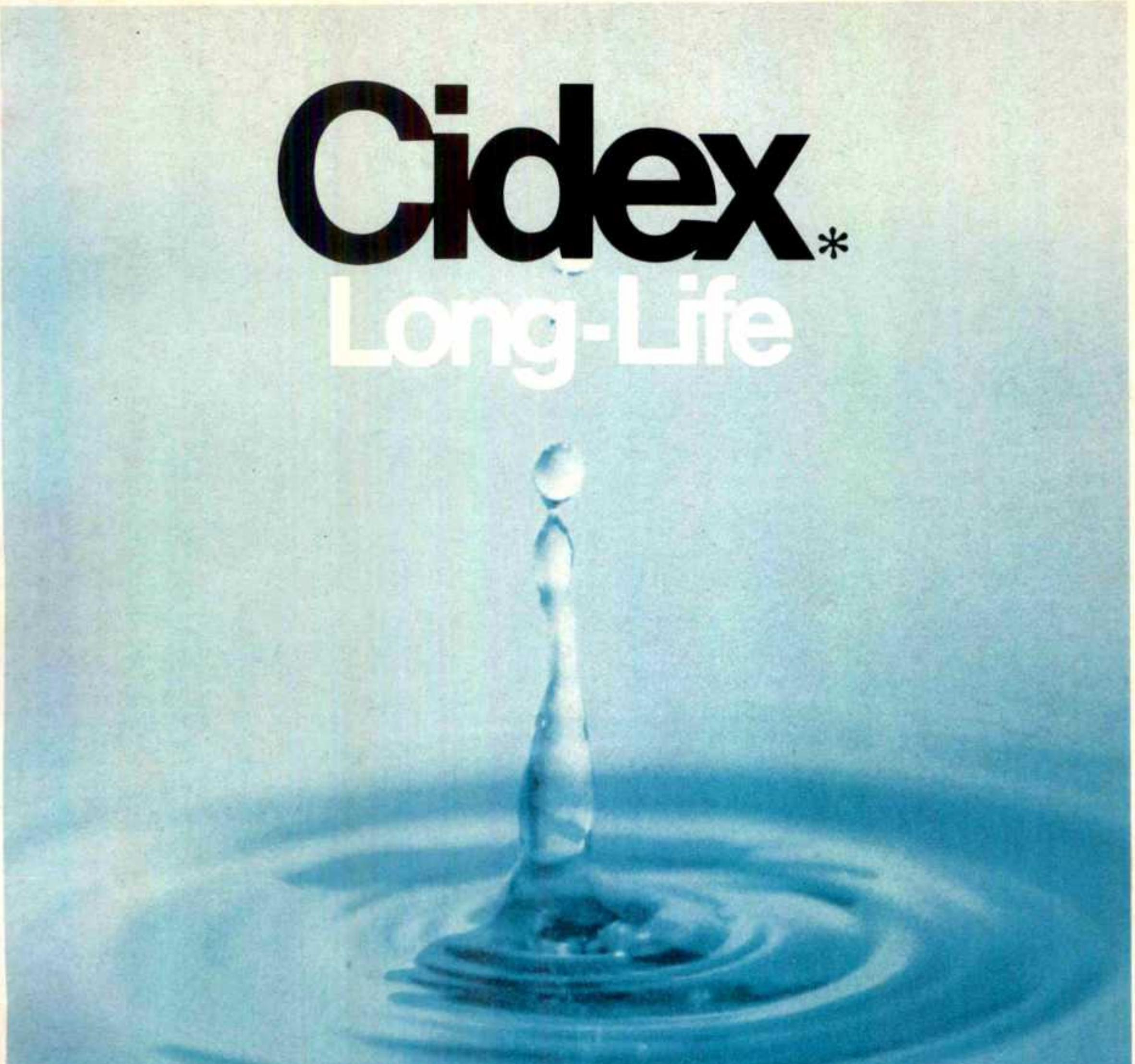

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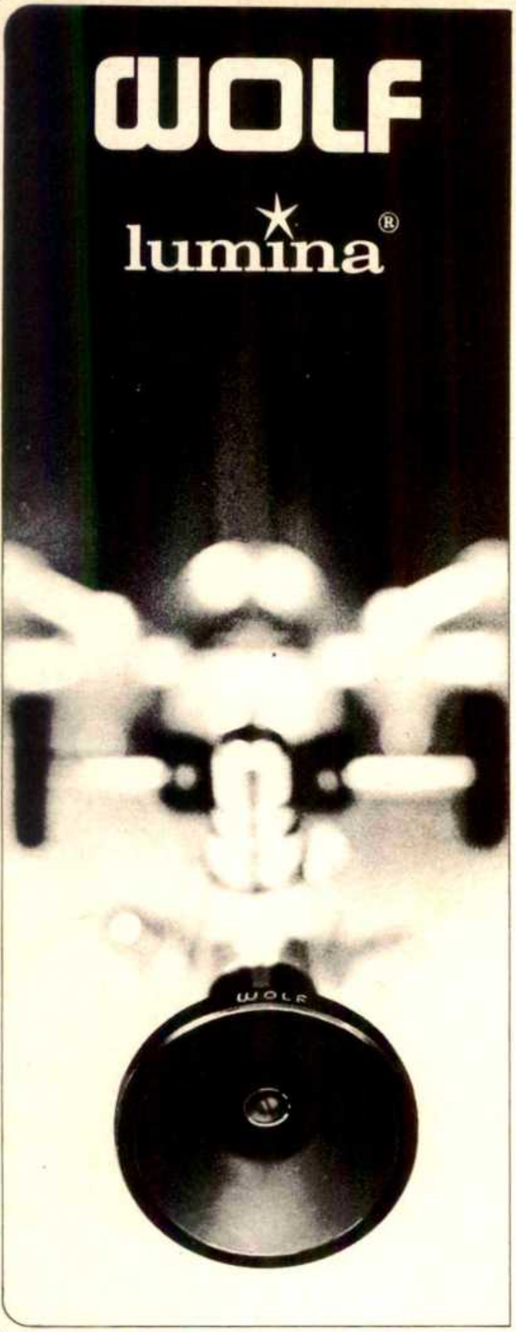

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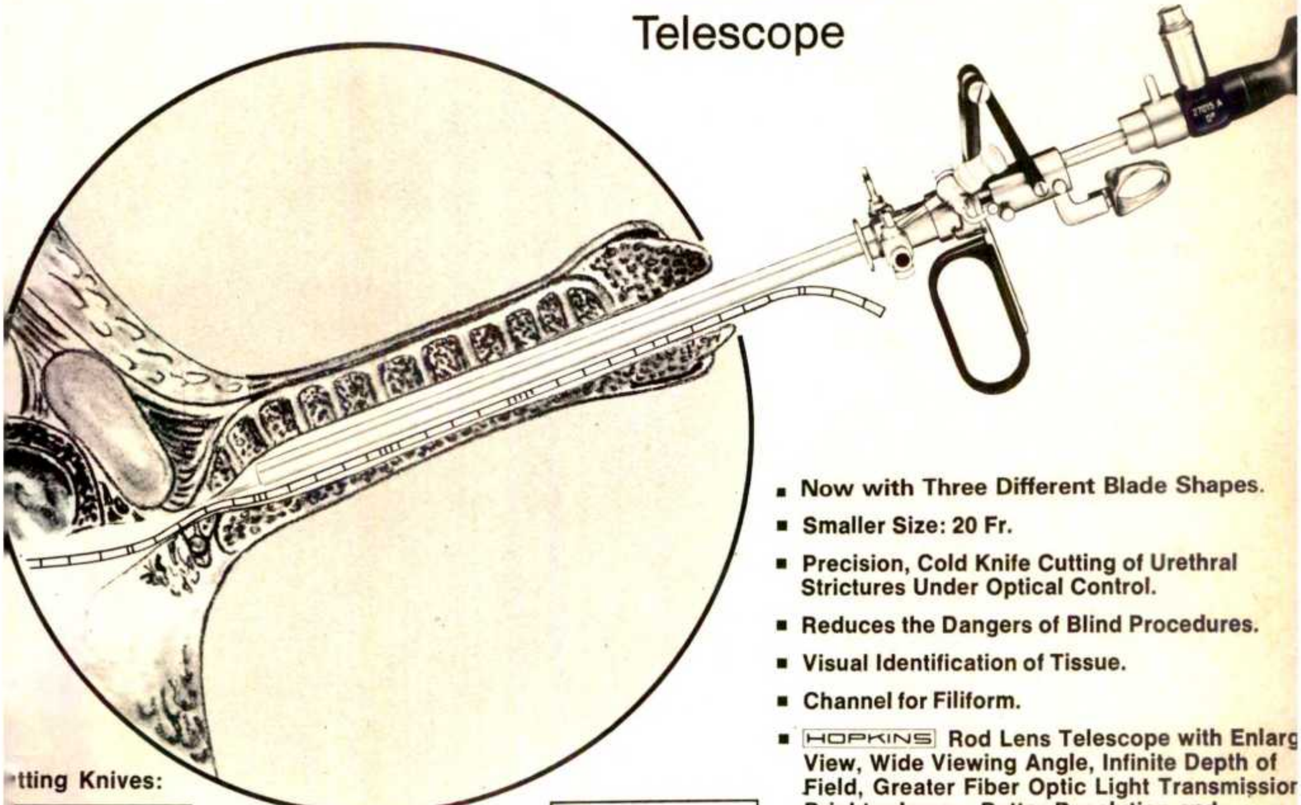

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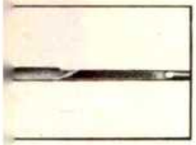

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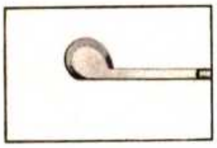

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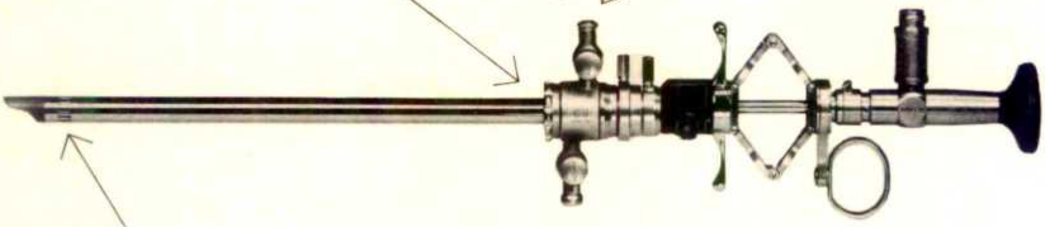

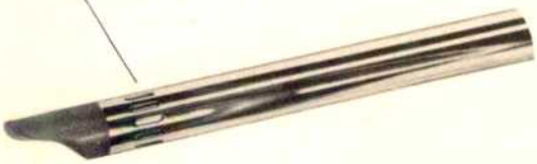

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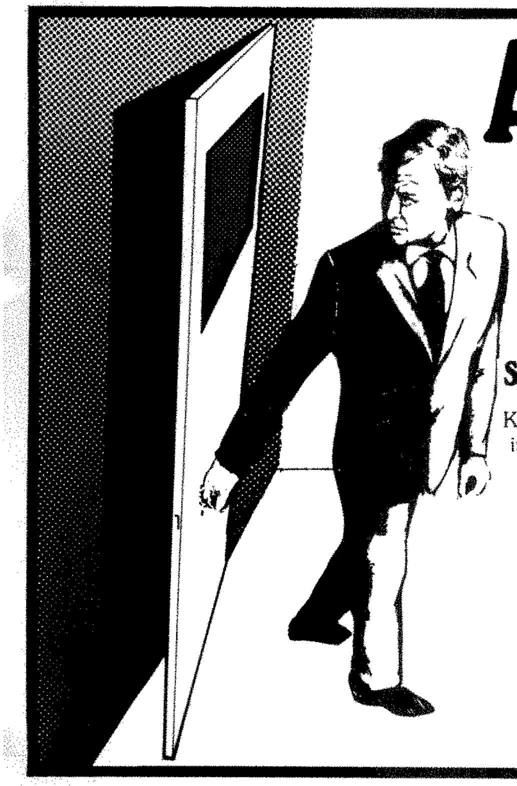

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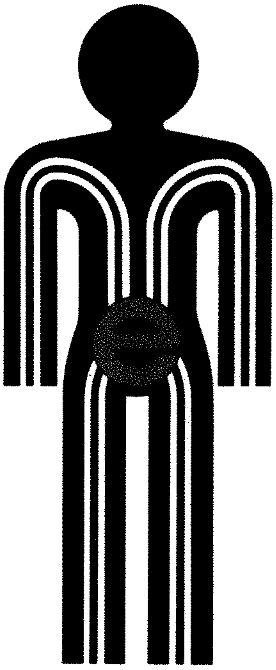

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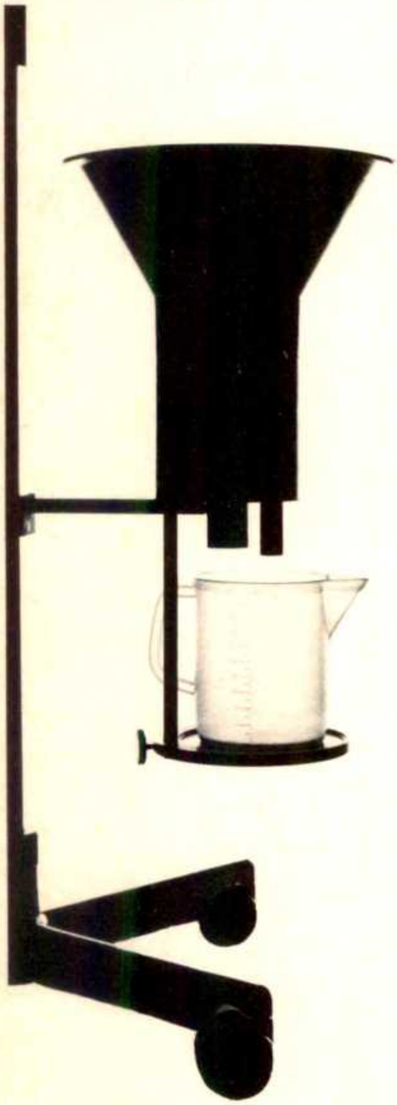

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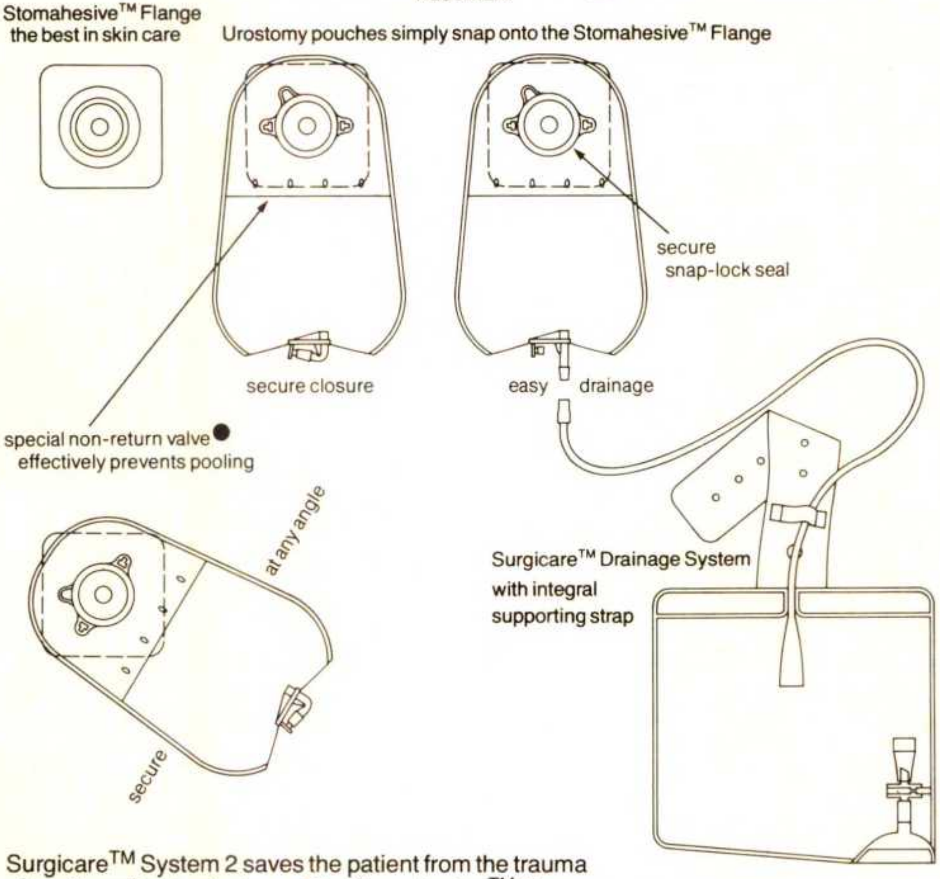
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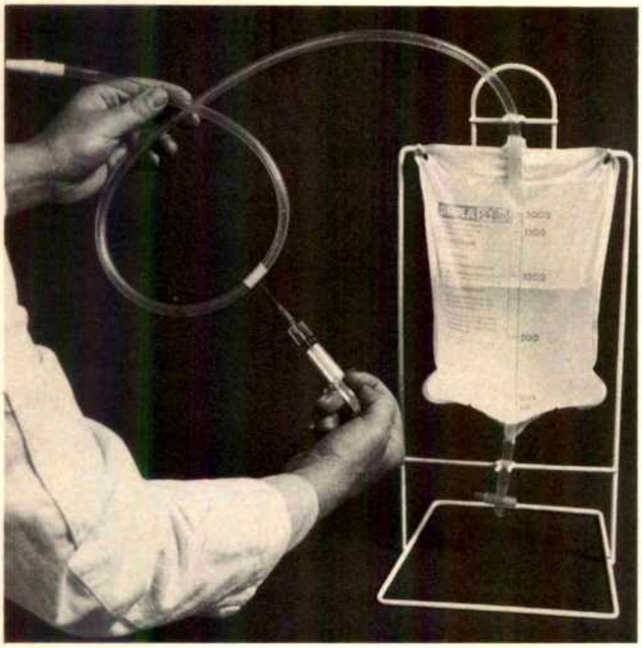

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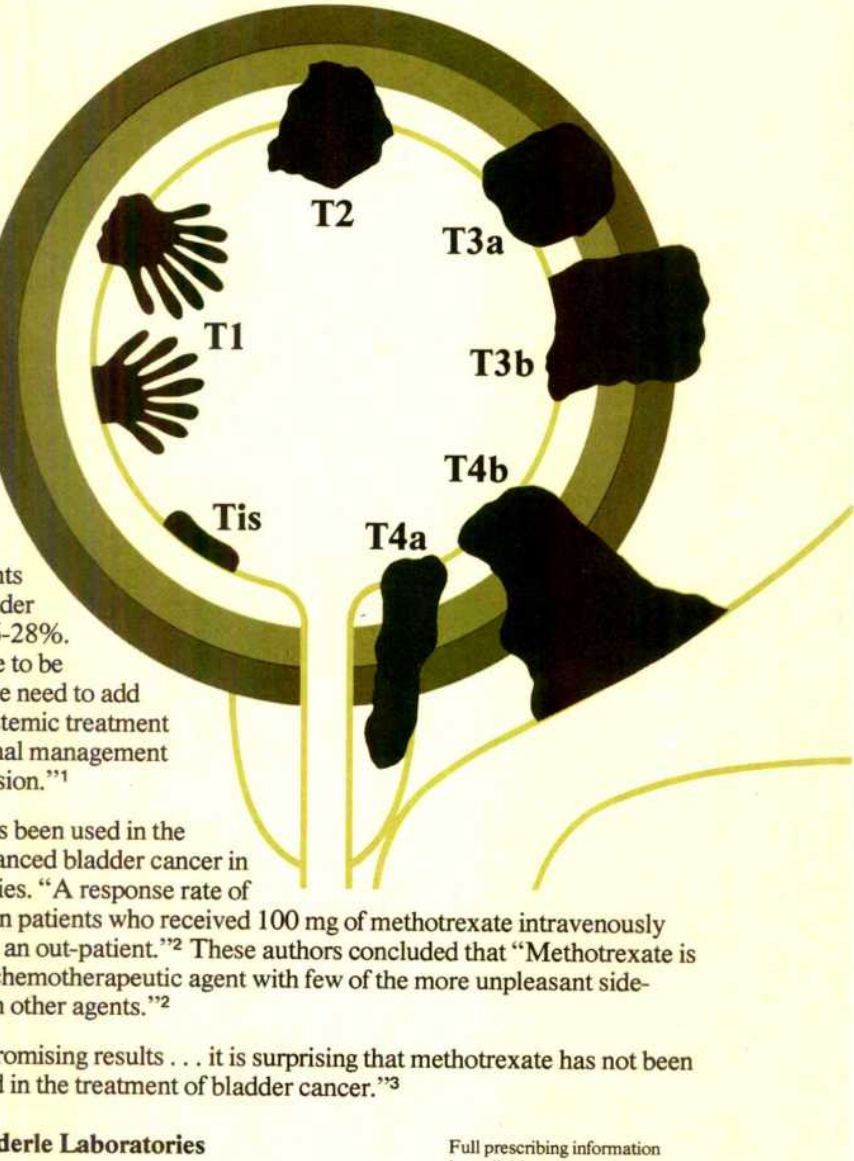
Methotrexate in advanced bladder cancer



The 5-year survival of patients with T2/T3 bladder cancer is only 16-28%. "If the results are to be improved then we need to add some form of systemic treatment to the conventional management of the primary lesion."[1]

Methotrexate has been used in the treatment of advanced bladder cancer in a number of studies. "A response rate of 56% was found in patients who received 100 mg of methotrexate intravenously every 2 weeks as an out-patient."[2] These authors concluded that "Methotrexate is a well-tolerated chemotherapeutic agent with few of the more unpleasant side-effects noted with other agents."[2]

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1. *Brit. med. J. 1977, 2, 1562*
2. *Brit. J. Urol. 1977, 49, 673*
3. *Cancer Res. 1977, 37, 2771*

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The Clinical Course in Patients with Renal Carcinoma Subjected to Extracorporeal Immunoadsorption

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Summary—The clinical course in 4 patients with renal carcinoma stages II, III or IV subjected to periods of extracorporeal immunoadsorption is reported. By this technique we have previously demonstrated that it is possible to isolate and remove circulating tumour associated antigens from the blood stream. The removal of these antigens should, according to present-day concepts, make it possible to control "antigenic inhibition" and/or "blocking", thus facilitating the immune mediated destruction of residual tumour cells in advanced disease. The clinical course in these patients, however, did not differ from the expected clinical course in other such patients. The failure of extracorporeal immunoadsorption to alter the natural course of the disease may be due either to too large a tumour burden or to the possibility that spontaneous tumours during evolution and progression become independent of immune restrictions.

According to current opinion, the immunotherapy of cancer should, in the future, involve one or more of the following approaches: (1) strengthening of the effector mechanisms of the immune response, (2) sensitisation of the tumour cells, or (3) elimination of "antigenic inhibition" and "blocking".

By using extracorporeal immunoadsorption with immunoglobulins, probably representing tumour specific antibodies (Irie *et al.*, 1974) eluted from renal carcinomas, it was possible to isolate 3 proteins which are not present in normal serum. Evidence from crossed immunoelectrophoresis using rabbit antisera against human whole serum proteins, renal carcinomas, or other tumour types as antibodies, followed by autoradiography, strongly indicated that these 3 proteins were tumour specific, probably representing tumour associated antigens (Langvad *et al.*, 1975).

It has been postulated that circulating tumour antigens or antigen-antibody complexes may occupy specific receptors of activated lymphocytes ("antigenic inhibition"), thus protecting the tumour cells from immune mediated destruction (Currie, 1973; Hellström *et al.*, 1973).

Therefore it might be anticipated that the removal of tumour specific antigens from the bloodstream by a series of extracorporeal immunoadsorptions would be able to control "antigenic inhibition" and "blocking", thus facilitating the immune mediated destruction of any residual tumour cells.

Four patients with renal carcinoma were subjected to one or more series of extracorporeal immunoadsorption. This paper is a report of the clinical course of the disease in these patients.

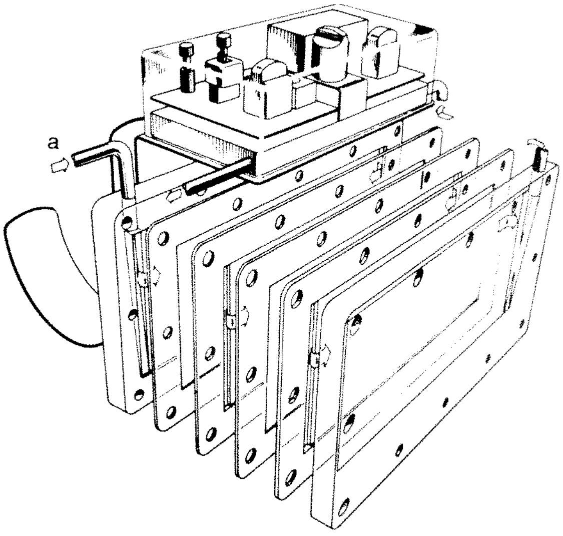

Fig. 1 Expanded view of extracorporeal perfusion chamber. Reprinted with permission of *British Journal of Cancer*.

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Materials and Methods

Patients

Patient A (P.B.A.S., 54-year-old male) had a right renal carcinoma and pulmonary metastases (stage IV according to the classification of Holland (1973)). Patient B (E.A.A.M., 55-year-old female) had a left renal carcinoma with lymphatic involvement (stage III). Patient C (P.O., 45-year-old male) had a right renal carcinoma with lymphatic involvement (stage III). Patient D (K.V.R., 63-year-old female) had a right renal carcinoma with capsular involvement (stage II). Two to 3 weeks following nephrectomy a Scribner shunt was inserted between the radial artery and a vein. The patients received daily doses of warfarin.

Perfusion Chambers

The extracorporeal perfusion chambers are made from optical quality polymethyl methacrylate and contain 23 0.9 mm thick 150 × 100 mm plates of the same material spaced 0.7 mm from each other (Fig. 1). The total surface of these plates is 0.5 m^2. The inlet (a) is equipped with a spreading device for the blood. This construction gives a laminar flow, and the narrow space between the plates ensures a good plate surface-blood contact. Each chamber contains a total of 150 ml of blood. The material and construction of the chambers ensure smoothness of the surfaces (so that few white cells or thrombocytes adhere to the surfaces during perfusion) and correct laminar flow at a velocity of at least 5 cm/s. The construction and properties of the extracorporeal perfusion chamber have been described previously (Hydén *et al.*, 1974).

Isolation of Immunoglobulins from Renal Carcinoma

Renal carcinomas obtained from other patients were cut in small pieces, rinsed briefly in water, homogenised in 4 volumes of phosphate buffered 15% NaCl (pH 7.4) and incubated for 2 h at 37°C on a magnetic stirrer. After centrifugation at 1000 g for 10 min the supernatant was saved and the procedure repeated. Immunoglobulins were precipitated from the combined supernatants by the addition of 250 mg NH_4 sulphate per ml. Subsequent purification of IgG and IgA was carried out as described by Ingild and Harboe (1973). This method implies that IgM is lost. The immunoglobulins were sterilised by Millipore (Millex) filtration and the protein content determined according to the method of Lowry *et al.* (1951).

Bonding of Immunoglobulins in the Chambers

The immunoglobulins from renal carcinomas are covalently attached to the polymer carrier via a silane derivative according to a technique modified according to Weetall (1970). The reagent solutions were pumped through the assembled chambers. The chambers were sterilised by 5% glutaraldehyde for one hour. This treatment also constituted the last step of the immobilisation procedure to activate the silane derivative. The chambers were then filled with sterile physiological saline containing streptomycin and placed at 4°C. This procedure ensured a valid covalent bonding of proteins to the plate surfaces. Thus in patients treated by L-asparaginase chambers no allergic reactions have been observed during or after perfusion for more than 400 h over a period of 2 years, nor could any antibodies against asparaginase be detected in the blood of these patients (Hydén *et al.*, 1974). The sterility of the perfusion chambers was continuously checked by bacteriological tests.

Extracorporeal Perfusion Procedure

Immediately before use the perfusion chambers were rinsed with 2000 ml of sterile physiological saline. The perfusion chamber was inserted into the blood circulation of the patient via the Scribner shunt, the last filling of the perfusion chamber being replaced by blood. At a systolic blood pressure of 130 to 170 mmHg, the blood flow through the perfusion chamber was 120 to 150 ml/min. Thus a pump was usually not required for its operation. A constant chamber temperature of 32 to 37°C during perfusion was maintained by immersion of the chamber in a water bath at 37°C. The duration of one extracorporeal perfusion was usually 3 to 4 h.

At the end of each perfusion period the arterial side of the Scribner shunt was clamped while physiological saline was infused into the chamber to press back into the circulation of the patient the 150 ml of blood remaining in the chamber. The arterial and venous sides of the Scribner shunt were then connected.

Elution of Proteins from the Chambers

The chamber was perfused with enough saline to

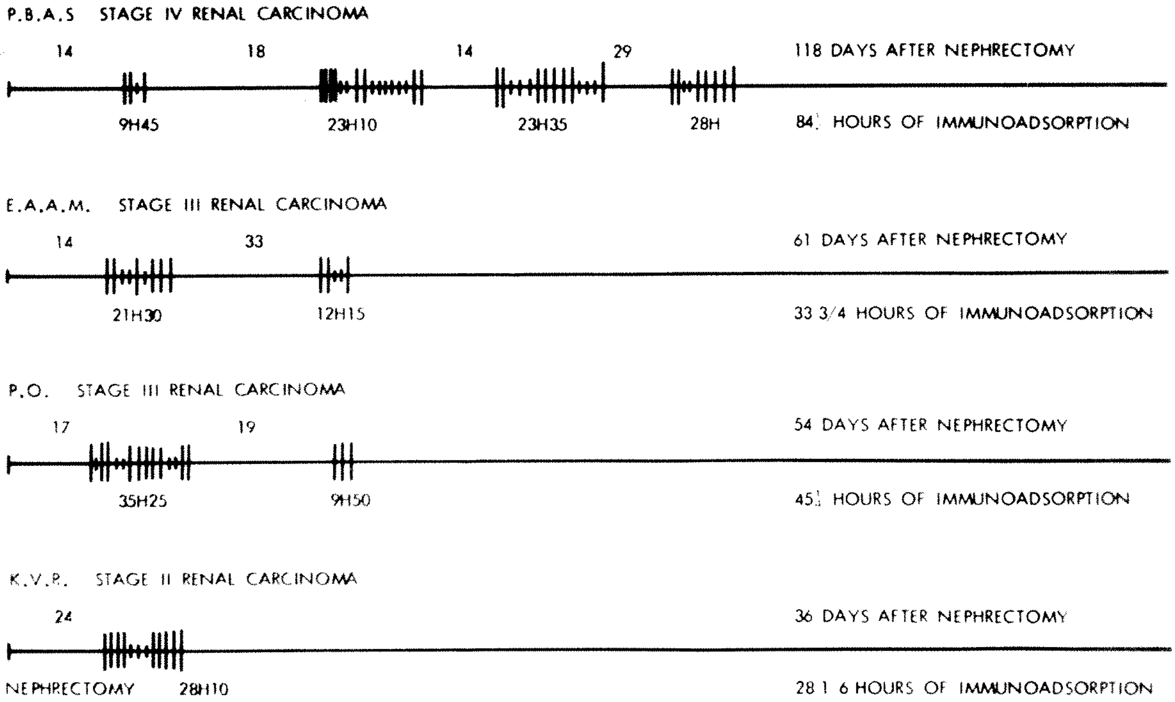

Fig. 2 Periods of extracorporeal immunoadsorption in 4 patients with renal carcinoma. ┼ indicates day on which extracorporeal perfusion was performed. + indicates day on which extracorporeal perfusion was not performed (usually Saturdays and Sundays). Figures below each line indicate total length of each perfusion period. Figures above each line indicate intervals (days) between each perfusion period and number of days after nephrectomy after which immunoadsorption was discontinued.

remove visible traces of blood. Few white cells or thrombocytes were observed adhering to the surfaces of the perfusion chambers. A fine greyish layer of protein was seen covering the surfaces.

The following steps were taken under sterile conditions to elute proteins caught on the chamber surfaces: 1000 ml of physiological saline were perfused through the perfusion chamber and collected, and this was followed by incubation at pH 7.4 with 0.25% trypsin (Difco) for 20 min at 18°C. As an alternative procedure the perfusion chamber was incubated at pH 2.8 (Tris-glycine) for 30 min at 18°C; 600 ml of Tris-glycine were then perfused and the pH of this perfusate was adjusted immediately to pH 7.0; 600 ml of physiological saline were then perfused and collected. After washing with an additional 2000 ml of saline, the eluted chambers were again ready for use.

Isolation and Identification of Eluted Proteins

These procedures have previously been described (Langvad *et al.*, 1975). It has been demonstrated that 3 of the 13 different proteins isolated from the perfusion chambers most likely represent tumour associated antigens.

Series of Extracorporeal Immunoadsorption

Each patient was subjected to periods of extracorporeal immunoadsorption as shown in Figure 2. The first period commenced 14 to 24 days following nephrectomy and each patient received 1 to 4 series of extracorporeal immunoadsorption with an interval of 14 to 33 days. During these perfusion periods, which lasted from 28 to 84 h, daily assessments of haemoglobin, white blood cells and thrombocytes, and differential counts of white cells, were carried out. Iron, transferrin, haptoglobin, protein electrophoresis, bilirubin, alkaline phosphatase, aspartate aminotransferase, and lactate dehydrogenase of serum or plasma were determined at regular intervals. During extracorporeal perfusion plasma free haemoglobin and haptoglobin were given.

Results

By using crossed immunoelectrophoresis with

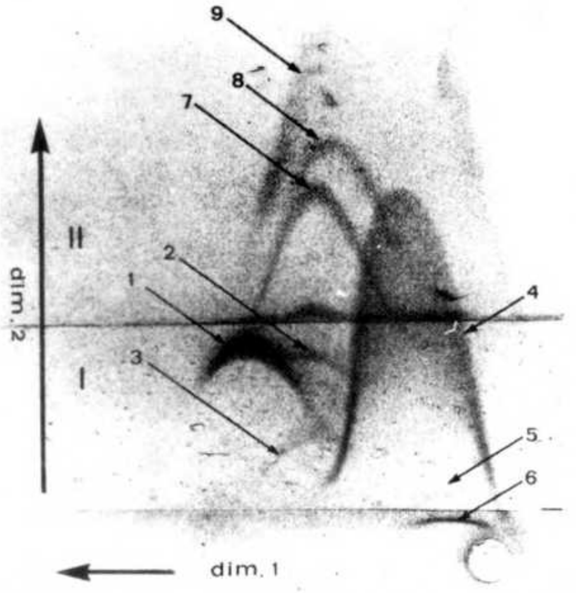

Fig. 3 Crossed immunoelectrophoresis with intermediate gel. Antigen: proteins eluted from perfusion chamber at pH 2.8. First dimension: 30 min, 8 V/cm. Anode to the left. Antibodies: I—rabbit antihuman whole serum protein. II—rabbit antirenal carcinoma. Second dimension: 18 h, 1 V/cm. Anode at the top. Staining: Coomassie brilliant blue R. Arrows on: (1) albumin, (2) α-1-antitrypsin, (3) α-2-macroglobulin, (4) complement C3, (5) IgG, (6) C3-activator, (7) protein A, (8) protein B, (9) protein C. Reprinted with permission of *British Journal of Cancer*.

intermediate gel as described by Axelsen *et al.* (1973) it was possible in all 4 patients to identify the same 3 proteins (Fig. 4) precipitated only by antirenal carcinoma antibody. The common nature of the precipitated tumour specific antigens was further emphasised by the fact that the homologous immunoglobulins bonded in the perfusion chamber and the heterologous antirenal carcinoma antibodies used in the crossed immunoelectrophoresis procedures were obtained from, and respectively raised against, different renal carcinomas, *i.e.* from patients different from the one subjected to extracorporeal immunoadsorption. Thus it may probably be concluded that renal carcinomas bear common tumour associated antigens.

During the periods of extracorporeal immunoadsorption the amount of this common tumour associated antigenic material isolated at each perfusion was determined semiquantitatively by crossed immunoelectrophoresis (Fig. 3). A gradual decrease and, after a few perfusions, a complete disappearance of the tumour associated antigens were noted in each patient. The absence of tumour associated antigens in the eluates of the chambers was also thought to indicate that the amount of circulating tumour associated antigen was significantly diminished and that it was possible, at least temporarily, to eradicate these tumour associated proteins from the patient's bloodstream. In patient A the amount of tumour associated material that could be eluted from the perfusion chambers increased after each interval between the perfusion periods. He was known to have pulmonary metastases and a continuous production of tumour associated antigens from these metastases was thought to account for their reappearance in the eluates from the perfusion chambers when the extracorporeal perfusion was resumed.

No changes were observed in the haemoglobin, white blood cells, thrombocytes and lymphocytes in patients B, C and D, indicating that no blood loss and no adherence of white cells or thrombocytes in the perfusion chambers resulted from the procedure. In patient A, who had advanced disease and impaired kidney function (creatinine 300 μmol/l), there was a gradual decrease in haemoglobin, so that he required several blood transfusions during the periods of extracorporeal immunoadsorption; there were no changes in white blood cells, thrombocytes or lymphocytes in this patient. On the second day of extracorporeal immunoadsorption he had a rigor and a sudden rise in temperature to 39°C which subsided spontaneously. No bacteriological explanation for this episode was found from the blood culture obtained, although the episode coincided with a rise in the white blood count. The extracorporeal immunoadsorption was not discontinued and no similar episodes occurred in this patient or in the other 3 patients.

Their clinical course is shown in Figure 4. Patient A (renal carcinoma stage IV) died from widespread metastases to the lungs as well as local recurrence 6 months following nephrectomy and 2 months after extracorporeal immunoadsorption. Patient B developed metastases to the supraclavicular lymph nodes and the vertebral bones 5 months after extracorporeal immunoadsorption, was treated with chemotherapy, but died from widespread metastases 2 years after nephrectomy. Patient C developed local lymph node recurrence 12 months after nephrectomy. Local lymphadenectomy followed by local radiotherapy was carried out. Distant metastases to the liver, lungs

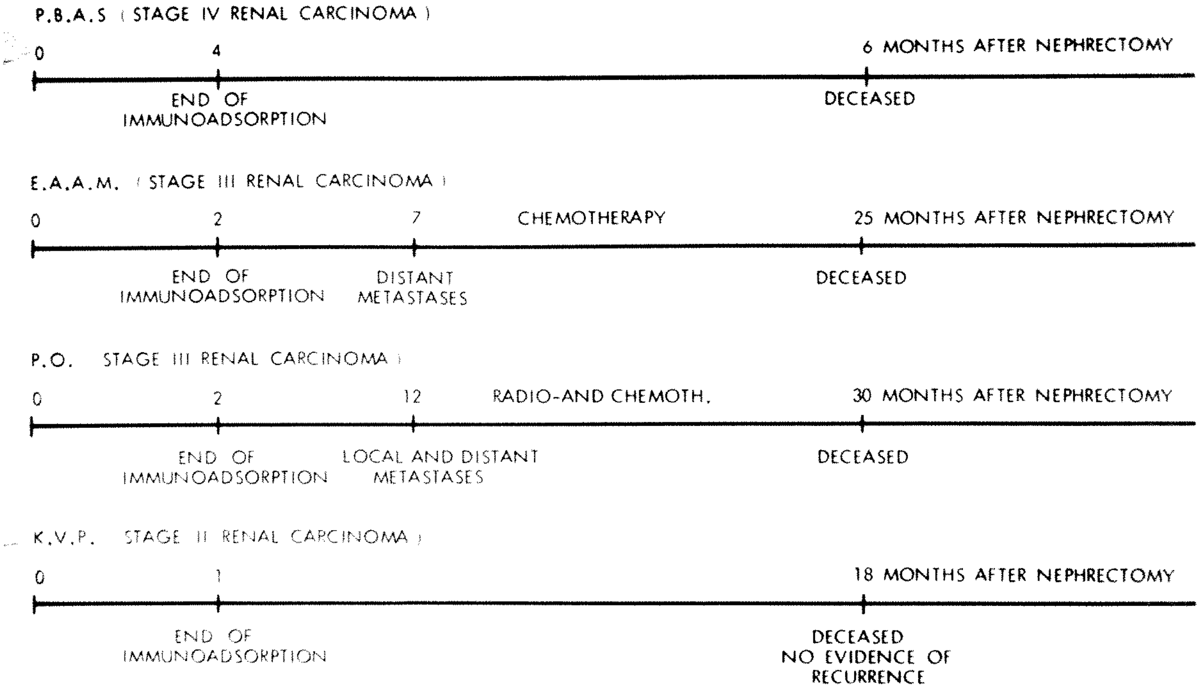
P.B.A.S (STAGE IV RENAL CARCINOMA)
0
4
6 MONTHS AFTER NEPHRECTOMY
END OF IMMUNOADSORPTION
DECEASED
E.A.A.M. (STAGE III RENAL CARCINOMA)
0
2
7
CHEMOTHERAPY
25 MONTHS AFTER NEPHRECTOMY
END OF IMMUNOADSORPTION
DISTANT METASTASES
DECEASED
P.O. STAGE III RENAL CARCINOMA)
0
2
12
RADIO-AND CHEMOTH.
30 MONTHS AFTER NEPHRECTOMY
END OF IMMUNOADSORPTION
LOCAL AND DISTANT METASTASES
DECEASED
K.V.P. STAGE II RENAL CARCINOMA)
0
1
18 MONTHS AFTER NEPHRECTOMY
END OF IMMUNOADSORPTION
DECEASED
NO EVIDENCE OF RECURRENCE

Fig. 4 Clinical course in 4 patients with renal carcinoma subjected to extracorporeal immunoadsorption.

and bones were observed shortly afterwards and treated with chemotherapy. The patient died from widespread metastases 30 months after nephrectomy. Patient D (stage II renal carcinoma) died from coronary artery occlusion 18 months after nephrectomy with no demonstrable local recurrence or distant metastases.

Discussion

The primary aim of extracorporeal immunoadsorption was to isolate tumour specific proteins from patients with carcinoma. In a previous publication (Langvad *et al.*, 1975) we have presented evidence that this goal has been reached, and the data indicate that these tumour specific proteins represent tumour associated antigens common for several renal carcinomas. The significance of these findings is further explored also in other tumour types.

Since our data indicated that it was possible to eliminate this antigenic material from the patients' circulation and since established concepts hold that the immune mediated destruction of residual tumour cells would be favoured by the removal of inhibiting and blocking tumour associated antigens, it was thought that extracorporeal immunoadsorptions might be beneficial for the patient with advanced renal carcinoma.

However, the clinical course in patients with advanced renal carcinoma (stage III or IV) subjected to periods of extracorporeal immunoadsorption did not differ from the clinical course observed in similar patients treated with surgery alone or with surgery and adjunctive radiotherapy and/or chemotherapy. Almost all patients with metastatic disease (stage IV) and about 60% of patients with lymph node involvement (stage III) are dead within 2 years of nephrectomy (Holland, 1973).

The clinical course in patient D with localised disease (stage II), in which the prognosis is more favourable, can also be considered following the natural course of operated renal carcinoma.

The failure of extracorporeal immunoadsorption to change the natural course of advanced renal carcinoma may be explained within the framework of the immune surveillance-escape theory. The size of the tumour burden may have been too large for the immune apparatus to combat even after the removal of inhibiting and blocking factors, or the elimination of "inhibiting" and "blocking" factors by immunoadsorption may not have been sufficiently effective. Since *in* *vitro* immunological tests such as cytotoxicity assays, leucocyte migration assays, lymphocyte transformation assays or quantification of T and B cells were not carried out in these patients, these questions are open to speculation. Another explanation of the apparent clinical failure may be sought in recent theories originating from observation of spontaneous tumours in animals, which suggest that during evolution and progression these tumours become independent of immune restrictions (Hewitt *et al.*, 1976; Klein and Klein, 1977).

Thus, tumour growth in patients with advanced renal carcinoma might be independent of the presence of circulating tumour specific antigens or immune complexes.

The question also arises whether extracorporeal immunoadsorption in these patients did in fact enhance residual tumour growth by interfering with host defence against residual tumour tissue. No definite answer can be given to that question, but extracorporeal immunoadsorption certainly did not induce any unexpected progression of the disease in patient D with localised tumour (stage II).

Acknowledgements

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Re-evaluation of Viability Testing of Cadaveric Kidneys for Transplantation

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Summary—Twenty-three human cadaver kidneys were studied during hypothermic pulsatile perfusion prior to transplantation. The accumulation of laevo-lactate and lactate dehydrogenase, alterations in pH and perfusion flow rate were measured and compared with organ function following transplantation. No parameter measured was found to be an accurate index of potential function.

It is a continuing source of concern that despite improved donor care and selection a significant number of kidneys never function following transplantation. Preservation by hypothermic perfusion provides an opportunity to study kidneys prior to transplantation and investigations have been undertaken to identify those that are severely injured. Measurement of metabolites, including glycolytic products, which appear in the perfusate of the stored kidney have been used to assess viability. The "lactate acidosis" measurable in perfusate has been suggested as an accurate index of viability (Johnson *et al.*, 1973a). Using the commercially available Gambro perfusion system, precise values have been suggested which identify kidneys that will function immediately following transplantation (Baxby *et al.*, 1974). Since these reports the perfusion system used (Gambro PF2) has been modified. Using this modified system, other workers have been unable to identify an accurate index of discrimination using perfusate laevo-lactate levels (Stephenson *et al.*, 1975; Modgill *et al.*, 1977). Because of the changes in methodology and the subsequent reports we have undertaken a re-evaluation of viability prediction by laevo-lactate values.

Materials and Methods

Renal Perfusion

Perfusion was carried out using the Gambro PF2D system with modified plasma protein fraction (PPF_2) as perfusate (Johnson *et al.*, 1973b). The machine was primed with 400 ml of perfusate and allowed to equilibrate at 8°C with a gas (98% oxygen/2% carbon dioxide) and perfusate flow adjusted to 200 ml/min.

Human cadaver kidneys were received both through the National Organ Matching Service and by local retrieval. Viability testing was carried out where a poor donor history or poor washout characteristics were reported or where such information was not available. All kidneys were inspected in a bowl of ice-cold saline and perinephric fat and connective tissues were removed. Any vascular injury was repaired and small polar vessels, when present, were anastomosed to the main renal artery. A suitable Gambro cannula was secured in the artery and connected to the prepared perfusion apparatus with the perfusate flow stopped. The flow was then gradually increased over a period of 10 min to achieve a pressure within the range of 40 to 60 mmHg; 8 ml samples were removed for analysis at the commencement of perfusion and at 60 min.

Perfusate Analysis

Perfusate laevo-lactate levels were measured using the Boehringer Lactate Combination Test Kit. Results were expressed as mmol/l of perfusate. Perfusate lactate dehydrogenase levels were measured using the Boehringer LDH Combination Test Kit. Results were expressed as units/litre of perfusate.

Extinction values were measured using the Unicam SP5000 spectrophotometer with careful temperature control.

pH was measured using the IL413 blood-gas analyser (Instrumentation Laboratories) at 37°C.

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Hydrogen ion concentration was calculated from pH values and expressed as mol/l of perfusate.

Flow rate was measured directly from the apparatus and expressed as ml/min. All estimations were made immediately following sampling.

Assessment of Renal Function

Twenty-three kidneys were assessed by perfusion, and renal function following transplantation was reviewed during the first week and at one year. Kidneys were divided into 2 groups according to function during the first week following transplantation:

Group 1. Immediate function, the recipient not requiring dialysis.
Group 2. Inadequate immediate function, the recipient requiring dialysis.

The need for dialysis was determined independently by the nephrologists who undertook the post-operative management. During the first week following transplantation no rejection phenomenon was severe enough to require dialysis support. One kidney was not included in this series because a period of post-operative hypotension due to haemorrhage from the arterial anastomosis impaired graft function. No kidney suffered impaired function as a result of systemic disease in the recipient.

The Mann-Whitney U test was used for statistical analysis.

Results

Clinical Data

Of the 23 kidneys studied 9 functioned immediately and 6 of these were still functioning at one year. Fourteen kidneys failed to function immediately; 7 of these were functioning at 4 weeks and 6 were still functioning at one year. Seven kidneys never achieved life-supporting function.

Table 1 Summary of Retrieval and Operative Data

Time		*Group 1*	*Group 2*
Warm ischaemia (min)	Mean	14.8	20.9
	SD	12.5	12.4
	n	9	14
Perfusion (h)	Mean	6.1	5.8
	SD	2.6	2.0
	n	8	14
Total hypothermia (h)	Mean	11.7	12.6
	SD	4.4	2.4
	n	9	14
Anastomosis (min)	Mean	25.9	29.9
	SD	11.3	10.3
	n	9	14

Table 2 Summary of Perfusion Data

Perfusate value		*Group 1*	*Group 2*
LDH units/l at 60 min	Mean	271.9	657.1
	SD	111.1	393.0
	n	9	14
Laevo-lactate mmol/l at 60 min	Mean	3.3	3.5
	SD	1.3	1.2
	n	9	14
Flow ml/min at 60 min	Mean	153	159
	SD	77	36
	n	9	11
pH fall over first 60 min	Mean	0.28	0.26
	SD	0.11	0.08
	n	5	12
Hydrogen ion rise mol/l × 10^{-7} over first 60 min	Mean	5.4	5.0
	SD	2.4	1.8
	n	5	12

Retrieval and storage data are shown in Table 1. The duration of warm ischaemia, the period between the end of normothermic perfusion in the donor and the commencement of hypothermia washout were not different in the 2 groups. Similarly, the period of hypothermic perfusion and total hypothermic storage time did not differ significantly. However, fewer kidneys failed to achieve life-supporting function when the total

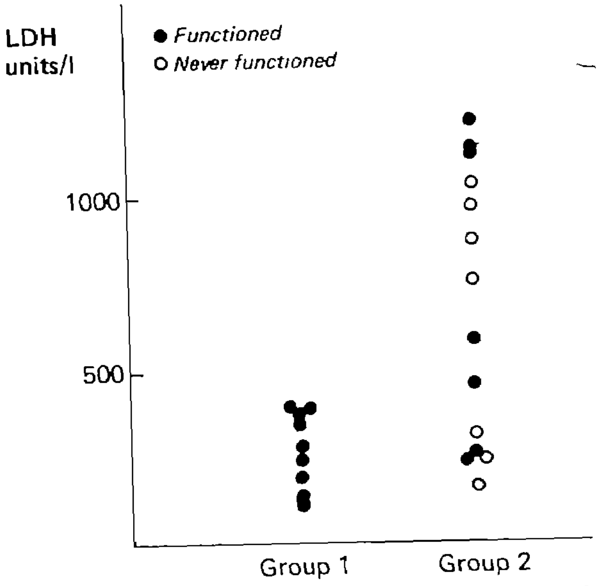

Fig. 1 Perfusion lactate dehydrogenase levels at 60 min and subsequent transplant function.

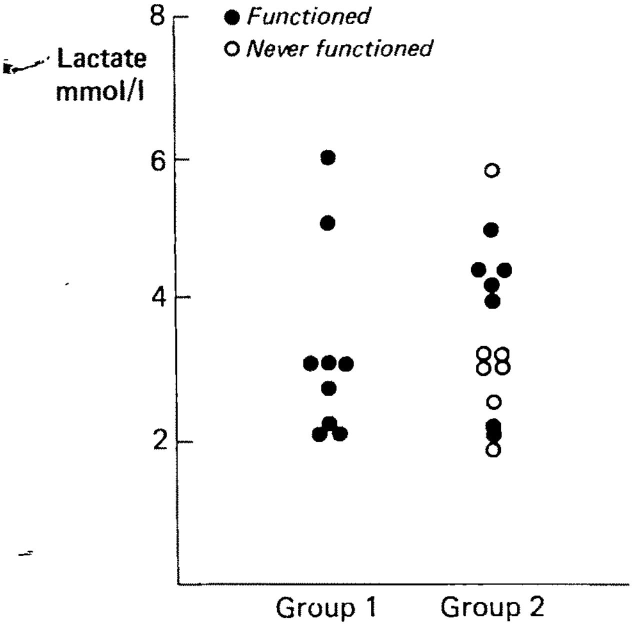

Fig. 2 Perfusion laevo-lactate levels at 60 min and subsequent transplant function.

hypothermic storage period was less than 12 h. Only one of the 10 kidneys stored for less than 12 h failed to function, whilst 6 of the 13 stored for longer periods never functioned.

Following viability assessment neither the period of perfusion preservation nor the time required to fashion the vascular anastomosis was found to be significantly different between the 2 groups.

Perfusion Data

Results of the perfusion parameters measured are shown in Table 2 and Figures 1 and 2.

Lactate dehydrogenase levels in the perfusate in Group 2 kidneys at 60 min perfusion time were significantly greater ($P = <0.05$) than in Group 1.

Laevo-lactate levels in the perfusate at 60 min were not significantly different between the 2 groups.

Flow rates within the permitted pressure range were not significantly different.

pH fall due to the accumulation of acidic products in the perfusate was not significantly different between the 2 groups. However, since there was some variation in the pH at the commencement of perfusion (pH range 7.080-7.305), comparison of pH differences did not accurately compare the changes in hydrogen ion concentrations. Changes in the measurable hydrogen ion concentration were therefore calculated and compared.

The increase in hydrogen ion in perfusate over 60 min perfusion was not significantly different between the 2 groups.

Discussion

Continuing development of the Gambro perfusion system to improve efficiency, compactness and economy has resulted in the earlier model (PF2) becoming obsolete. Changes introduced after a satisfactory method of viability prediction was reported (Baxby *et al.*, 1974) have included the use of interface oxygenation in place of a membrane oxygenator. This improved system (PF2D) requires a smaller volume of perfusate. Metabolites arising from the kidney during perfusion therefore yield a higher concentration in the perfusate, whilst the mass of substrates available for continuing metabolic activity is decreased when the improved system is used.

The release of cytoplasmic enzymes during ischaemia has been studied in the assessment of renal viability (Belzer *et al.*, 1968). LDH is released into the perfusate, probably as a result of cellular membrane disruption. In this study we have demonstrated greater LDH levels and thus presumably a greater degree of cellular injury in those kidneys which did not function immediately. In common with other workers (Stephenson *et al.*, 1975; Modgill *et al.*, 1977), we have found a wide range of values with overlap between the 2 groups. Whilst no kidney yielding an LDH value greater than 400 μ/l functioned immediately, the exclusion of kidneys with values greater than this would have deprived 5 patients of a transplant which eventually functioned satisfactorily. In addition, 3 of the 7 kidneys which never functioned would still have been transplanted. Thus LDH levels are unsatisfactory as an index of viability.

The concentration of glycolytic products of metabolism in perfusate during assessment is influenced by the accumulation of anaerobic metabolites in the kidney during ischaemia. In addition, lactate is produced by continuing metabolic activity during perfusion. Hypothermic metabolic activity is dependent upon the mass of substrate available and may be influenced by the presence of other metabolic intermediates. In common with more recent publications (Stephenson *et al.*, 1975; Modgill *et al.*, 1977), we have been unable to demonstrate any relationship between lactate levels in perfusate and human cadaveric kidney viability. Indeed, the adoption of any arbitrary discriminating value would deprive more patients of a satisfactorily functioning transplant than it would protect from receiving a kidney which never functioned.

Acknowledgements

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A Technique for Hemiacidrin Dissolution of Renal Stone Complicating an Ileal Conduit

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Summary—A technique for dissolving a renal stone complicating an ileal conduit is described. Free ureteric reflux was present, which allowed retrograde irrigation of the stone by infusion of hemiacidrin solution into the ileal conduit. With careful attention to urine infection and the pressure within the system, this technique might be applicable to other patients in whom free ureteric reflux is present and pyelolithotomy, percutaneous nephrostomy or the passage of ureteric catheters is difficult.

Patients with ileal conduits and other urinary diversion procedures commonly develop renal stones (Schmidt *et al.*, 1973) and urinary tract infection is an important predisposing factor in the development of this complication (Dretler, 1973; Grimes, 1975). Patients often undergo a series of operations for removal of recurring renal stones, and this makes subsequent surgical intervention progressively hazardous or extremely difficult. Free ureteric reflux is also a common complication in patients with ileal conduits (Schmidt *et al.*, 1973; Bergman *et al.*, 1978), especially when non-reflux operative procedures have been used to create the urinary diversion.

A new technique is described for hemiacidrin irrigation and dissolution of a renal stone in a patient with an ileal conduit in whom free vesicoureteric reflux was present.

Patient and Methods

The patient, a 25-year-old male, was born with flaccid paraplegia and neurogenic bladder due to meningomyelocele. Gross bilateral vesicoureteric reflux was present, and since birth he had had recurrent symptomatic urinary tract infections.

At 13 years of age bladder stones were removed and later a large staghorn calculus was removed from his left kidney. Urinary diversion of both ureters through an ileal conduit was performed. By 20 years of age a further staghorn calculus was removed from his right kidney and since that time he had had a functionless hydronephrotic right kidney. Despite intensive antibiotic therapy, recurrent urinary infections persisted and a further staghorn calculus developed in the left renal pelvis.

At the age of 25 years his renal function deteriorated rapidly (serum creatinine 0.20 mmol/l to 0.54 mmol/l over a period of 13 weeks). The decline in renal function was associated with progressive dilatation of the left renal pelvicaliceal system and intractable urinary tract infection. A limited exploration revealed no obstruction to either ureteric orifice in the conduit, but the left kidney was noted to be firmly incarcerated in fibrous tissue and removal of the calculus or nephrostomy was technically not feasible. A retrograde ileal loopogram confirmed free ureteric reflux outlining the renal calculus on the left. This made dissolution of the calculus with hemiacidrin by infusion of the solution into the ileal conduit possible.

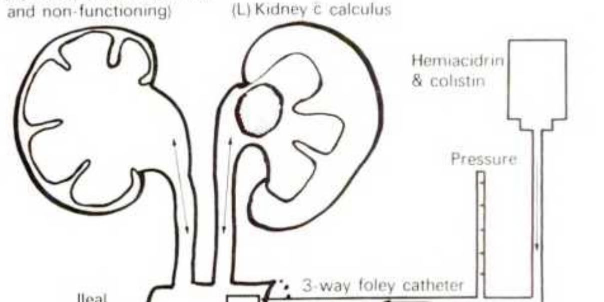

Fig. 1 System for infusion of hemiacidrin.

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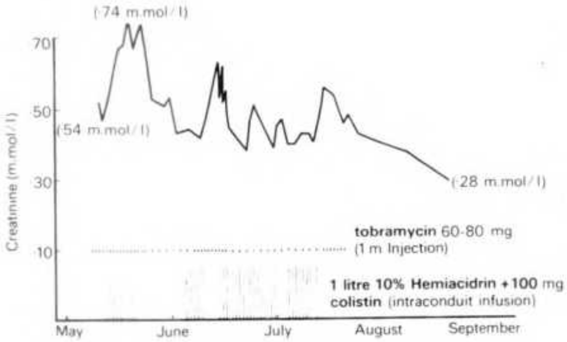


Fig. 2 Clinical course and details of treatment.

Method of Infusion of Hemiacidrin

A solution of 10% hemiacidrin containing 100 mg of colistin per litre was infused through one arm of a 3-way Foley catheter (30 ml balloon) (Fig. 1). The balloon was positioned into the ileal conduit and held against the internal aspect of the stoma by a 100 g weight exerting traction on the catheter. The outflow arm of the catheter was connected to a urinary drainage bag. A water manometer was attached to the inflow circuit and, with the outflow clamped, hemiacidrin solution was infused slowly until a pressure of 20 to 30 cm of solution was attained. At this point the infusion was stopped and the solution left in the conduit for one hour. The solution and any urine were then allowed to drain to the urinary drainage bag by release of the clamp. A pressure of 20 to 30 cm of solution was chosen because it had been shown radiologically to cause adequate ureteric reflux to surround the stone, but at 35 to 40 cm of pressure the patient regularly experienced pain. He was able to terminate an infusion at any time and was encouraged to do so if pain was experienced during the infusion.

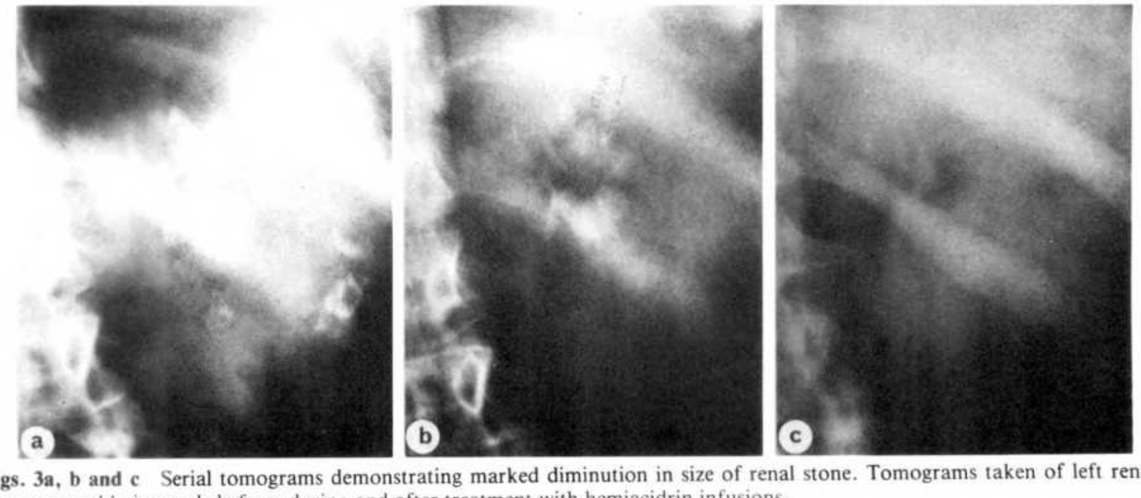
The infusion procedure was repeated 6 to 8 times daily (not at night) using 150 to 200 ml of solution for each instillation. A daily total of one litre of hemiacidrin solution was used and the process continued intermittently for 2 months during daylight hours.

In addition, oral and intravenous fluids were used to promote a urine output in excess of 5 l per day. It was intended that this large urine volume would flush away fragments of stone and aid the dissolution. A parenteral antibiotic (tobramycin) was used to suppress systemic infection as the urine was infected at the time of treatment (organism *Klebsiella pneumoniae*—sensitive only to tobramycin and colistin). The progress in treatment of this patient is summarised in Figure 2.

Results

Serial tomograms (Figs. 3a, b and c) showed a marked reduction in size of the stone during treatment. Multiple fragments were recovered from the urinary drainage bag and analysis of these fragments showed the chemical composition to be calcium, ammonium, magnesium and phosphate.

One week after commencement of hemiacidrin infusions the renal function had deteriorated (serum creatinine 0.74 mmol/l). However, over the 2-month treatment period there was a gradual improvement and even after cessation of hemiacidrin infusion improvement in renal function



Figs. 3a, b and c Serial tomograms demonstrating marked diminution in size of renal stone. Tomograms taken of left renal area at monthly intervals before, during and after treatment with hemiacidrin infusions.

continued for 6 weeks, then stabilised (serum creatinine 0.28 mmol/l) (Fig. 2).

Urinary tract infection (*Klebsiella pneumoniae*) persisted after the treatment had ceased. Presumably the organism was lodged deeply within the calculus matrix and complete dissolution had not occurred when the hemiacidrin infusions were stopped.

Discussion

Hemiacidrin was first discussed in 1959 by Mulvaney, who later demonstrated (1960) that it could be used to dissolve renal stones by irrigation. This experience was confirmed by others, but the danger of septicaemia in patients with urinary infection was rapidly appreciated (Auerbach *et al.*, 1963; Fostvedt and Barnes, 1963). Nemoy and Stamey (1976) reported impressive results with dissolution of infective stones, and especially in the prevention of their recurrence after surgery, provided that there was meticulous attention to control of urinary infection. Prevention of outflow obstruction is also of great importance (Fam *et al.*, 1976). Irrigation with hemiacidrin solution has usually been performed through either intra-operative nephrostomy (Jacobs and Gittes, 1976), percutaneous nephrostomy (Dretler *et al.*, 1979) or through ureteric catheters (Nemoy and Stamey, 1971).

Urinary diversion procedures are commonly associated with the presence of ureteric reflux and the placement of nephrostomy tubes may be difficult in such cases. This technique used the free ureteric reflux in this patient to irrigate the renal stone, which showed a dramatic diminution in size. Perhaps more importantly, there was an associated improvement in renal function, almost certainly due to relief of obstruction.

Our limited experience suggests that the use of an appropriate systemic antibiotic (and perhaps antibiotic also in the washout solution) is necessary during this method of irrigation, particularly in the presence of established infection. The irrigation procedure could easily lead to introduction of bacteria into the circulation. Attention should also be paid to the hydrostatic pressure of the infusion, since the occurrence of pain might be due to excessive pressure in the system.

It is concluded that this technique might be considered in other situations where free ureteric reflux is present, thus allowing free irrigation of renal stones.

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Sequestration of Ureteric Segments in Dogs

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Summary—In 2 separate series of dogs a segment of ureter was isolated from both bladder and kidney and left *in situ* with an intact blood supply. Tense cysts formed in these sequestered segments regardless of whether the ends were occluded or the segments were split longitudinally and left open. The formation of these cysts can be prevented by the removal of the urothelium. The cyst contents were found consistently to have a sodium concentration below that of the simultaneously obtained serum concentration and urea concentration higher than the simultaneously obtained serum urea. Osmolalities and protein levels within the cysts were virtually identical to the serum levels.

Duplication of the ureter is a common problem in paediatric urology. In such patients the upper pole of the kidney is often severely dysplastic and its ureter often drains abnormally into the bladder, with either a ureterocele or a severe degree of reflux. In the past, these children have had a heminephrectomy and excision of the whole of the ureter draining the dysplastic segment. Unfortunately, the 2 ureters of a duplex pair have a common blood supply and total excision of the abnormal ureter can result in inadvertent damage to the blood supply of the normal ureter. To prevent this, Johnston (1972) suggested the operation outlined in Figure 1. This operation entails a heminephrectomy and the removal of as much of the abnormal ureter as is possible without threatening the blood supply to the good ureter. The anomalies that require correction at the lower end of the ureter would then be dealt with on their merits, and again that portion of the abnormal ureter which could easily be excised without risk to the blood supply of the normal ureter would be removed. The segment of abnormal ureter remaining would then be split and left sequestered: that is, separated from both bladder and kidney, but with an intact blood supply.

The fate of sequestered ureteric segments in dogs is reported in this paper.

Materials and Methods

Two groups of mongrel dogs weighing between 6 and 18 kg were anaesthetised with thiopentone, intubated, and maintained on a nitrous oxide, oxygen, and halothane mixture sufficient to maintain adequate anaesthesia and oxygenation.

Group A—5 Dogs

These dogs were anaesthetised and the bladder opened through a midline lower abdominal incision. The procedure performed is outlined in Figure 2. On each side the ureter was dissected free from the bladder wall, preserving the blood supply arising from the bladder and also, where possible, any vessel running parallel to the ureter.

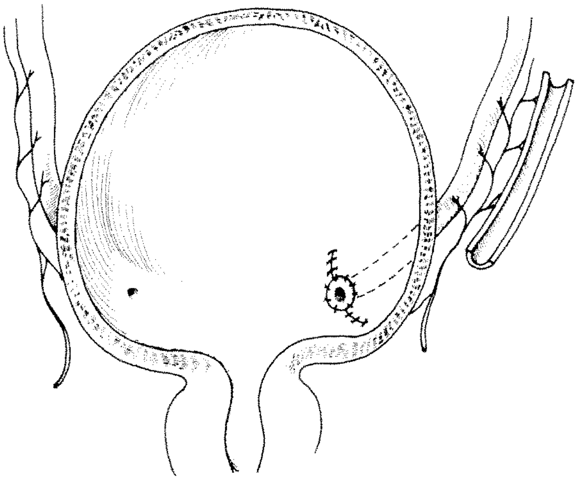

Fig. 1 A diagram of the procedure suggested by Johnston. Points to note: (1) The common blood supply to both the normal ureter and the segment of ureter to be sequestered arising from branches of the vesical vessels. (2) The ureteric segment is trimmed but the mucosa is left *in situ*.

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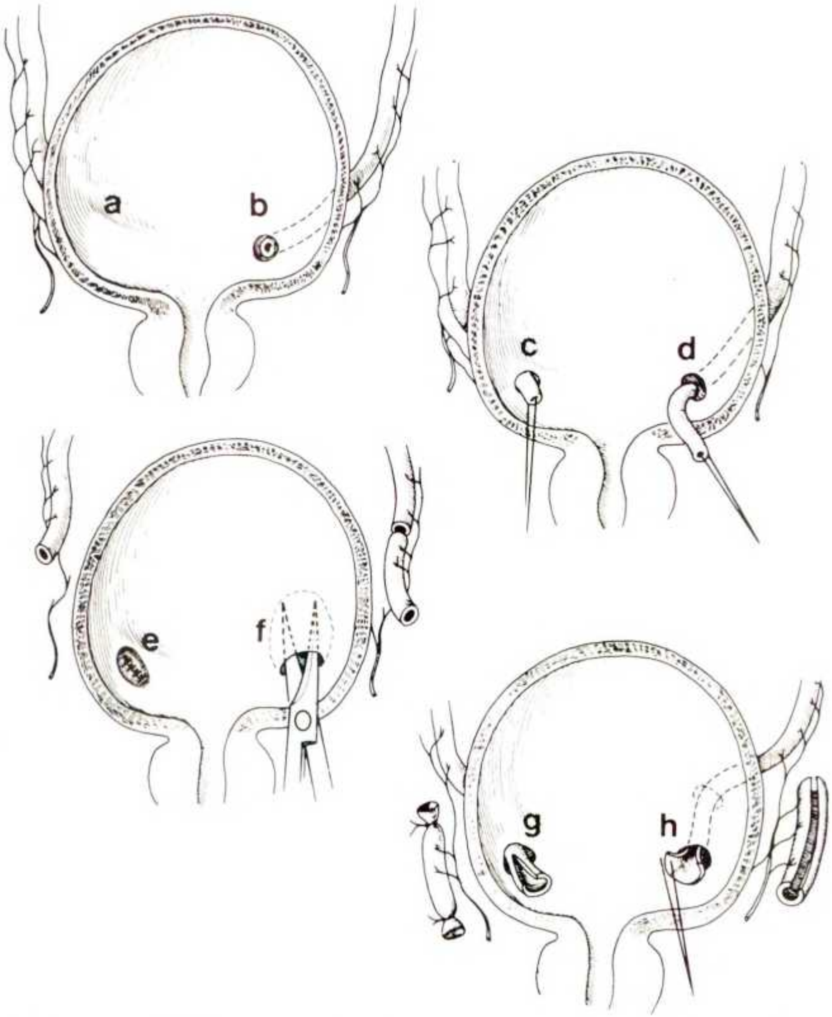

Fig. 2 Operative procedure in group A dogs. The normal ureteric orifice (a) is circumcised (b). (c) A traction suture is placed in the tip of the ureter. (d) Dissection close to the ureteric wall is continued through all layers of the bladder wall. The ureter is then taken outside the bladder wall (e) and the defect in the bladder musculature is closed. (f) The ureter is divided 2 to 3 cm from its end, taking care to preserve the blood supply to the segment to be sequestered and also to the remainder of the ureter. A submucosal flap is raised and a new entrance for the ureter through the muscle wall is created. The remaining ureter is brought through this newly created submucosal tunnel (g). (h) The end of the ureter is spatulated. Mucosa-to-mucosa anastomosis is carried out using 5/0 Dexon or chromic catgut. The sequestered segments are either tied at both ends as in (g) or split from end to end as in (h), taking care to preserve blood supply.

This isolated segment of ureter was then retained outside the bladder and the proximal intact ureter was reimplanted using an antireflux technique. Mucosal anastomosis was carried out with 5/0 Dexon or 5/0 chromic catgut suture. On each side, therefore, there remained a segment of ureter with an intact blood supply, lying free in the peritoneal cavity, but connected to neither bladder nor kidney. The blood supply was then assessed and the segment that was deemed to have the best blood supply was split along its antimesenteric border. The segment on the opposite side was occluded at either end with a silk ligature or by application of metal clips. The ends of this segment were marked with either silk sutures or the application of metal clips. The bladder was then closed over an 18 FG Malecot catheter with 2 layers of 3/0 chromic catgut. The catheter was led out through the abdominal wall through a separate stab incision and the abdominal incision was closed in 2 layers with interrupted 1/0 chromic catgut. Intramuscular administration of penicillin and streptomycin was started during the operation and was continued for 5 days. The dog's head was kept in a device designed to prevent the dog from pulling out the catheter until it was removed on the fifth post-operative day.

Group B—6 Dogs

In this group the surgical procedure was virtually identical to that outlined above except that the 2 sequestered segments were both split from end to end along the antimesenteric border. The segment which was deemed to have the best blood supply had 0.5 ml of saline solution injected into the submucosal plane and the mucosa was completely removed. The ends and the edges of both of these segments were then marked with metal clips, and the bladder and abdomen closed as before. The post-operative progress of the sequestered segments was followed on serial X-rays taken in the antero-posterior and lateral projection at weekly intervals for 4 to 6 weeks.

Observations at Sacrifice

The dogs from both series were sacrificed at intervals ranging from 3 weeks to one year. At the time of sacrifice the dog was again anaesthetised as for the initial operation. Samples of blood, urine and whatever fluid was found in the sequestered segments of ureter were taken and the dog was then sacrificed. The samples were analysed for sodium, potassium, chloride, urea, and osmolality in the Chemical Pathology Laboratory of The Royal Children's Hospital. The methods used were as follows: sodium and potassium were estimated on a flame photometer. Chloride was measured on a colorimetric titrator designed specifically for small samples. Osmolalities were measured on an electronic semi-micro osmometer. Urea was measured according to the procedure outlined by Fawcet and Scott (1960) and Henry (1964).

Results

Group A

Regardless of whether the segments had been split or the 2 ends occluded, large tense cysts developed (Fig. 3) measuring up to 4 cm in the longitudinal axis and containing up to 13 ml of a rather turbid fluid. The cysts were well formed by 3 weeks and persisted for a year (Fig. 4). The histology of these cysts revealed that the epithelium and muscle walls were intact in those segments in which the ends had been occluded (Fig. 5), but in those segments that had been split, there was a consistent defect in the muscle wall which was filled with fibrous tissue and covered by a normal epithelium (Fig. 6). Cysts did not form in 2 cases. In one, a segment of ureter was noted to have doubtful viability at the time of sequestration and this progressed to scar formation. In another dog a seg-

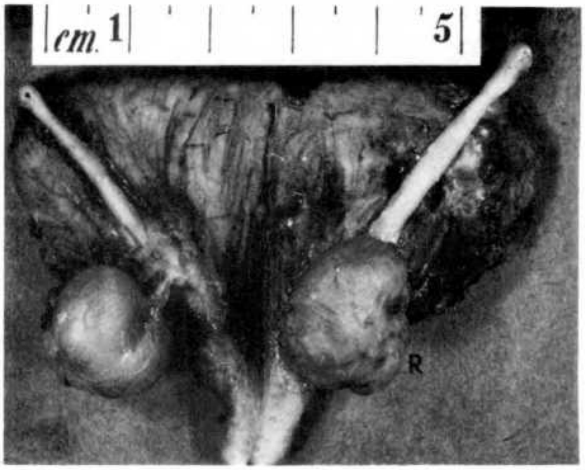

Fig. 3 Bladder, ureters and cysts from dog 205A. Sacrificed 7 weeks post-operatively. The bladder has been opened and is viewed from behind. The sequestered segment on the right was split from end to end; that on the left was tied at both ends.

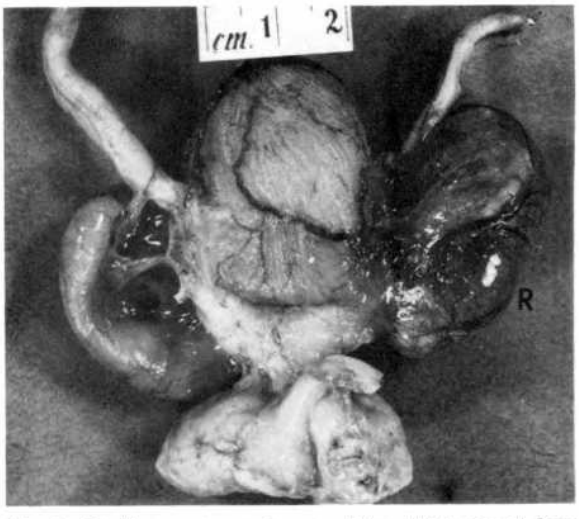

Fig. 4 Bladder, ureters and cysts of dog 198A viewed from behind. Sacrificed at 1 year. The segment on the right began as a 2 cm section of ureter split from end to end. At autopsy this contained 13 ml of fluid. The segment on the left was 3 cm long initially and was tied at both ends. This cyst contained 6 ml of fluid at autopsy.

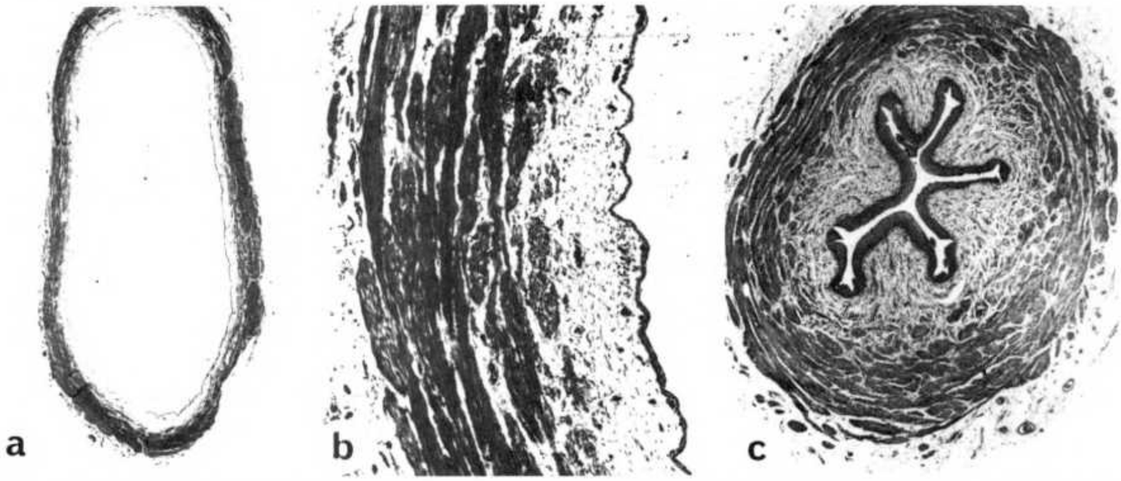

Fig. 5 (a) Cyst formed from a segment occluded at both ends (Masson's trichrome ×11: 1 year post-operatively). Epithelium and muscle are continuous around the circumference of the cyst. (b) High power view from a segment of the wall of the cyst in (a) Masson's trichrome (×100). Note the hypertrophy of the muscle fibres and the flattened but intact transitional epithelium. Compare normal dog ureter (c). (c) Normal dog ureter (Masson's trichrome ×50). Compare the total bulk of muscle in this ureter with that shown in (a) and (b).

ment that had been occluded at both ends was found at autopsy to look like a slightly dilated segment of ureter. In most instances the cysts contained 1 to 2 ml of turbid fluid, containing amorphous debris and scattered inflammatory and epithelial cells. The levels of electrolytes, urea, protein and the osmolalities of the fluid within the cysts are outlined in Table 1. It often proved impossible to measure all of the desired parameters on the small volumes available.

Group B

In this group no macroscopic cyst formed in any segment from which the mucosa had been removed. In one dog a small strip of mucosa had been left behind and this formed a microscopic

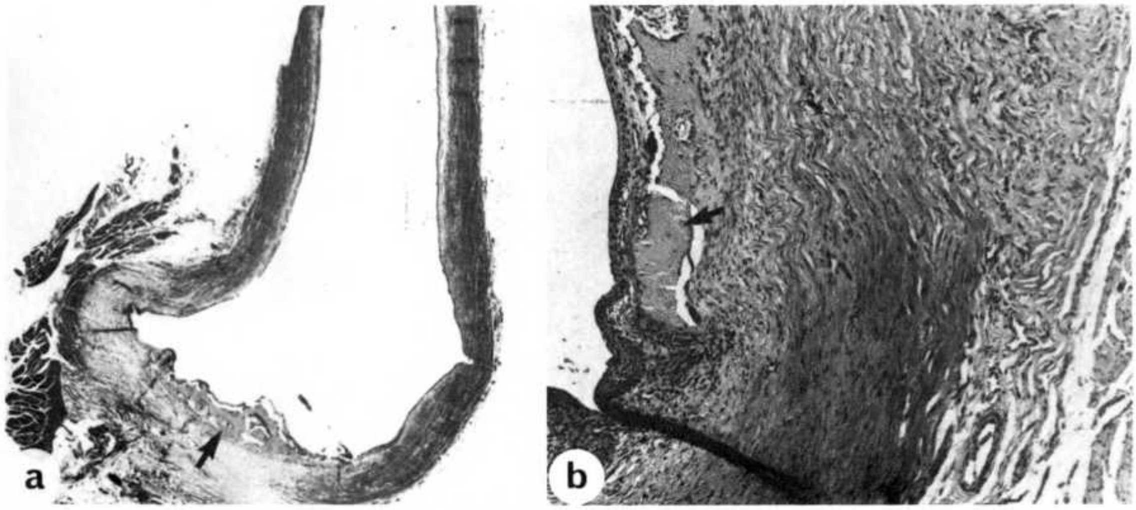

Fig. 6 (a) Section from a segment that had been split from end to end (Masson's trichrome ×9.5). The group of muscle fibres at the left of the figure are bladder wall muscle fibres. There is a clear gap in the muscle coat of this cyst filled by fibrous connective tissue. Bone has formed immediately subjacent to the epithelium at the site of the scar (→). Similar deposits of bone were sometimes found at the site of the ureterovesical anastomosis. (b) High power view (Masson's trichrome ×100) showing the muscle coat ending at the bottom of the picture and scar tissue continuing on. Well formed transitional epithelium overlies well developed bone (→), 8½ weeks post-operatively.

Table 1 Group A. Contents of Cyst

Dog no.	Period of sequest. weeks	Diameter of cyst (cm)		Cyst levels						Blood levels						Urine levels				
		L	R	Na	K	Cl	U	Os	Prot	Na	K	Cl	U	Os	Prot	Na	K	Cl	U	Os
229	3	2.1	2.5	L 139 R 124	4.0 6.0	118 113	9.4 9.2			147	3.8	114	6.5			17	54	77	20.2	
205	7	1.6	2.0	No levels						No levels						No levels				
249	7	1.25	1.1	R 131	2.6	116	10.7		44	150	5.1	112	8.3			216	79	193	1200	
200	26	—	3.0	R 115	6.3	89	9.9			143	4.2	116	5.5			51	25	68	84.5	
198	51	4.2	3.8	L 135 R 146	5.8 4.2	114 119	9.3 7.9	305 295	16 51	147	4.1	118	4.9	300	59	133	43	143	610	1100

Na = Sodium millimoles/litre.
K = Potassium millimoles/litre.
Cl = Chloride millimoles/litre.
Os = Osmolality milliosmoles/kg water.
Prot = Protein g/litre.
U = Urea millimoles/litre

Table 2 Group B. Contents of Cyst

Dog no.	Period of sequest. weeks	Side with mucosa intact	Diameter of cyst (cm)	Cyst levels						Blood levels						Urine levels				
				Na	K	Cl	U	Os	Prot	Na	K	Cl	U	Os	Prot	Na	K	Cl	U	Os
234	7	R	1	130	12.7	118	8.6			148	3.6	115	5.2	305	57	35	51	56		>1600
237	7	R	1.6	139	9.2	109	7.0	290	42	144	4.4	111	5.4			108	68	138	600	
283	7	R	1.1	132	11.7	112		295		143	4.0	114	13.2	290	62	7	14	19		400
284	7½	L	1	No levels						No levels						No levels				
220	8½	L	1.9	133	9.8	113	10.2		46	148	4.2	118	6.8	260	57	61	20	70	249	500
251	9	R	0.75	128	12.0	111	8.6		50	148	4.4	113	7.6	300	23	13	53	63	819	1120

Na = Sodium millimoles/litre.
K = Potassium millimoles/litre.
Cl = Chloride millimoles/litre.
Os = Osmolality milliosmoles/kg water.
Prot = Protein g/litre.
U = Urea millimoles/litre.

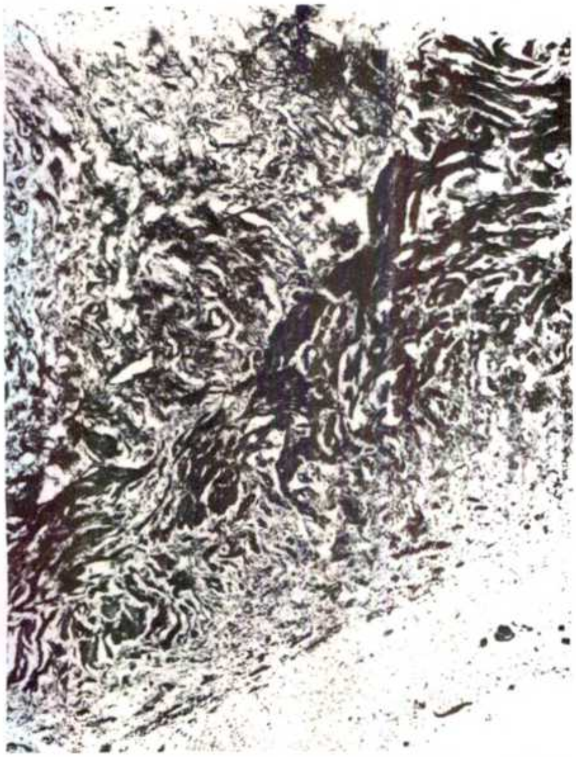

Fig. 7 Smooth muscle sandwiched between layers of fibrous connective tissue following the complete stripping of the mucosa (Masson's trichrome × 50) 8½ weeks post-operatively.

cyst. All of the other segments from which the mucosa had been removed showed, at autopsy, a layer of smooth muscle sandwiched between 2 layers of fibrous connective tissue (Fig. 7). In none of these segments was the viability of the smooth muscle in doubt. In those segments in which the mucosa was not removed, a cyst formed in all dogs. These dogs were followed post-operatively with serial X-rays in the antero-posterior and lateral projections. In those segments that were going to form a cyst, the metal clips marking the segments were seen to move closer together in the first 2 weeks post-operatively. Virtually no further movement was noted thereafter (Fig. 8). Those segments from which the mucosa had been stripped showed virtually no movement of the clips over a period of 4 weeks. At autopsy the cysts were identical to those found in Group A, but the clips were usually found protruding into the cyst cavity (Fig. 9). The histology of the cysts was identical to that described for the split segments in Group A. The levels of electrolytes, protein and urea, and the osmolality of the contents of the cysts are outlined in Table 2. Again, the incomplete results reflect the small volumes available for study.

Discussion

These experiments demonstrate that a sequestered segment of ureter (that is, a segment attached to neither bladder nor kidney, but with an intact blood supply) will form a cyst if its mucosa is intact. The epithelium appears to play a primary role in the development of these cysts, since removal of the epithelium prevents cyst development. In the light of authoritative statements in current physiology texts, this is surprising. Pitts (1974) relegates the ureters and bladder to "conduit and temporary storage functions respectively." Kiil and Setekleiv (1973) devote a single

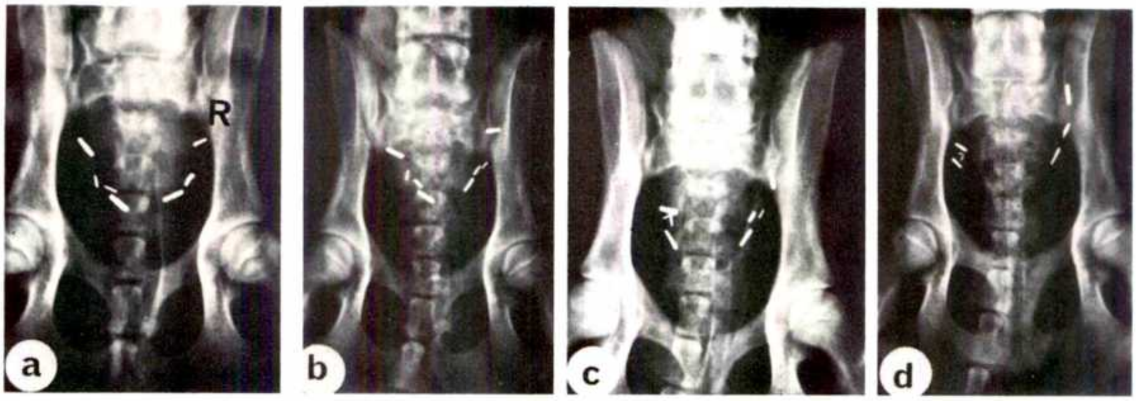

Fig. 8 Radiographs at weekly intervals in dog 251. (Antero-posterior view) (a) immediately post-operatively, (b) 1 week later, (c) 2 weeks post-operatively, (d) 4 weeks post-operatively. The mucosa was stripped from the segment on the left. The clips marking the segment remain virtually stationary over the 4-week period. Those on the right remain stationary for the first 2 weeks post-operatively and maximum movement takes place between the 14th and 21st days. On the original radiographs the larger clips on the right move from 12 mm apart immediately post-operatively to 6 mm apart by 4 weeks.

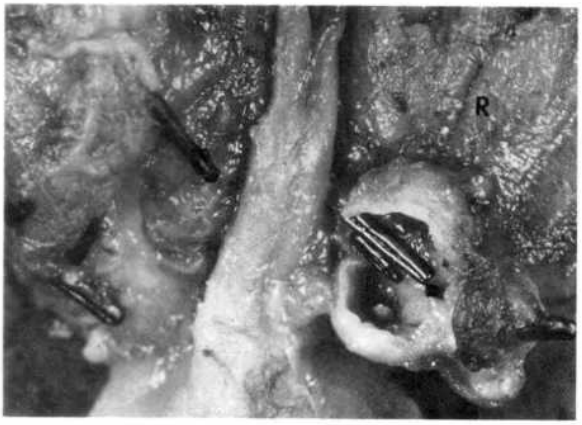

Fig. 9 Posterior view of the bladder and cyst of dog in Figure 8. The strip of smooth muscle can be seen lying between the clips on the left and clips can be seen lying within the cyst cavity on the right.

paragraph to the role of the urothelium. They quote Boyarsky (1964) as suggesting an active transport process to explain the impermeability of the urothelium to water and electrolytes. Boyarsky postulates an active transport for some ions but offers no proof to support this theory. The bulk of the literature supports the concept of the mammalian urothelium as a relatively inert epithelium, providing an impermeable barrier with little movement of substances across it either into the lumen of the bladder or from bladder lumen to blood. Cooper (1972) states that the epithelium is extremely stable, with an individual lifespan of each constituent cell in excess of 200 days. He also notes that after a surgical injury the urothelium proliferates rapidly and that this proliferation continues beyond the time of the injury. The resulting hyperplastic state persists for some time after the surgical insult has passed. The majority of authors, including Hicks (1966) and Turnbull (1973), agree that there is minimal passive diffusion across the epithelium. In the light of these statements it seems strange that such an inert epithelium behaves in a manner so similar to other actively secreting epithelia.

Latchem (1922) created hydronephroses in dogs by partial or complete obstruction of the distal ureter and later performed a nephrectomy on the affected side, leaving a segment of partially or totally obstructed dilated ureter behind. He found that such segments of ureter persisted indefinitely, even if the distal obstruction was complete. The mucosa in these segments remained healthy and the muscle coats became hypertrophic. The contents of the cystic segments of ureter were not examined.

That a free graft of urothelium transplanted into an ectopic site forms a cyst has been known for a long time. Axhausen, in 1913, performed free grafts of gastric and bladder mucosa into the peritoneal cavity of dogs. He found that autotransplanted gastric and transitional epithelium both formed cysts within 16 days. The ultimate size of the cyst appeared to be directly related to the size of the original graft and the length of time it was left *in situ*. Huggins (1931) transplanted sheets of urothelium into the rectus sheath of dogs and other animals. He measured the calcium, phosphorus and carbon dioxide content and the pH of the cyst fluid. The pH in general was lower than serum pH, and the calcium and phosphate levels were higher than simultaneously obtained serum levels. No other constituents of the cyst fluid were measured. The cysts persisted for up to 267 days.

Harada *et al.* (1959) attempted to create an artificial bladder by a free graft of urothelium into the rectus sheath in dogs. They found that it formed a cyst within 3 weeks, but it degenerated within 4 months. The cysts were repeatedly injected with Urografin, and it is not clear whether this contributed to the degeneration. However, if a functioning ureter was inserted into the cyst at 3 weeks a cutaneous fistula forming a poor bladder resulted and the urothelium persisted indefinitely. No levels of urea or electrolytes from within the cysts were recorded.

The consistent findings of marked differences in the concentrations of urea and sodium within the cysts found in these experiments support Boyarsky's suggestion of an active transport mechanism for at least some substances across the urothelium.

The mechanism by which the edges of the sheet of sequestered ureter contract is also of interest. Since Davis, in 1943, first described his intubated ureterotomy for treatment of ureteric strictures, there has been considerable controversy as to the relative roles of scar contraction and smooth muscle regeneration in the healing of such a ureterotomy. In a series of experiments by Oppenheimer and Hinman (1955, 1956) and by Hinman and Oppenheimer, (1956, 1957a, b), the role of the normal passage of urine past the healing ureter was clearly defined. Their work was confirmed by others including Hamm and Weinberg (1956) and Lapides and Caffrey (1955). In 2 experiments a barrier of fine mesh tantalum or loops of stainless steel wire was laid in the path of the "regenerating" smooth muscle of the healing ureter (Oppenheimer and Hinman, 1955) or a previously constructed bladder tube (Hinman *et al.*, 1963), and some evidence of smooth muscle regeneration was found. However, in most of their experiments the barrier laid down was insufficient to prevent smooth muscle from being pulled between the loops of wire or the interstices of the mesh by the forces of scar contracture. The authors also ignored the possibility that longitudinal scar contracture pulled smooth muscle fibres around the ends of the barrier that they had placed. However, in a minority of the experiments there were some subtle changes in the staining characteristics of some of the smooth muscle fibres that could have been due to smooth muscle regeneration. Weaver (1957, 1958) also felt that regeneration of smooth muscle played an important part in the reconstitution of the healing ureterotomy.

Against these findings are the findings of Mahoney *et al.* (1962) and Boyarsky and Duque (1955), who showed that there was longitudinal contraction of the healing ureterotomy both in the presence of a splint (Boyarsky and Duque, 1955) and in the absence of a splint (Mahoney *et al.*, 1962).

In the present study the clips marking the edges of a sheet of sequestered ureter moved closer together in the first 2 weeks and then remained virtually stationary. It appears that in the sequestered ureter, wound contraction (rather than contracture of established scar tissue) at the edges of the sheet of ureter plays a major role in the development of the cyst. However, as demonstrated in Figure 5, there is certainly muscle hypertrophy and possibly hyperplasia in the established cyst.

One unresolved question is the long-term fate of such sequestered cysts. Intermittently over the years there have been reports of infections and primary carcinomata arising in the ureteric stump following a nephrectomy. The primary carcinoma arising in the ureteric stump appears in most cases to be especially anaplastic and aggressive. Taylor and Berry (1954) report one case in which there was incomplete excision of the carcinoma arising in a ureteric stump. The patient presented with metastatic disease 6 months after the removal of this carcinoma and died of metastases within 8 weeks of the discovery of the metastatic disease. There is a possibility that patients in whom a segment of ureter has been sequestered may develop, even years after the operation, an aggressive, anaplastic, transitional cell tumour. Because of this risk, this author recommends that patients in whom a segment of ureter has been sequestered be examined by ultrasound to detect any possible cyst and that either these cysts be excised completely or their mucosa removed.

It is concluded that sequestered segments of ureter form cysts which are well established by 3 weeks and persist for at least a year. The epithelium plays a major role in the development of these cysts and their formation in a sequestered segment of ureter can be prevented by removing the epithelium. There is some evidence that the urothelium is not as inert as was once thought but that the living urothelium can secrete fluid. The epithelium in a sequestered segment of ureter may give rise to an aggressive transitional cell carcinoma.

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Vesicoureteric Reflux Following Renal Transplantation: a Simple Method of Ureteric Implantation

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Summary—We have used a simple method of ureteroneocystostomy in renal transplant patients. This entails a no-tunnel "drop-in" with a long free segment protruding into the bladder lumen. The incidence of vesicoureteric reflux was investigated in 81 transplant patients who had a follow-up period ranging from 4 months to 15 years (mean 3.7 years); 29 of these patients had recurrent urinary tract infections. Micturating cystography demonstrated reflux in 6 patients (7.4%). In these 6 patients the presence of reflux had no deleterious effect on renal function and the infections were easily controlled with long-term antibiotics. In the 52 patients without urinary infection no reflux was demonstrated.

The conclusions based on this study indicate that (1) in the absence of recurrent infection there are no indications for micturating cystography and (2) this method of ureteroneocystostomy is expedient and has a low incidence of reflux.

The incidence of urological complications following renal transplantation varies from 5 to 12% (Bewick *et al.*, 1974; Debruyne, 1977). Mortality and morbidity rates from urinary fistulae are especially high in the early post-transplant period owing to high doses of immunosuppressive agents which impair tissue healing and interfere with the host's ability to resist infection. Vesicoureteric reflux is less well documented but it could lead to progressive graft failure because of the combined effects of recurrent urinary infection and back pressure on the renal tubules.

The usual method of restoring continuity of the urinary tract in renal transplantation is by some form of ureteroneocystostomy. High anastomoses (pyeloureterostomy and ureteroureterostomy) have largely been abandoned, since the urological complications are twice as common as with a low ureter-bladder anastomosis (Debruyne, 1977). Standard methods of ureteric implantation adopt either an external anastomosis as advocated by Calne (1976) or a transvesical submucosal tunnel (Politano and Leadbetter, 1958). The former procedure dispenses with a cystostomy and requires a shorter period of bladder drainage. Other authors (O'Donoghue *et al.*, 1971; Whittier *et al.*, 1974; Debruyne *et al.*, 1978) favour ureteric implantation without an antireflux mechanism, claiming equally acceptable results.

A simple no-tunnel "drop-in" ureteroneocystostomy has been used in this unit for nearly 20 years. We have determined the incidence of vesicoureteric reflux and its relationship to recurrent urinary tract infection and allograft function.

Materials and Methods

Eighty-one unselected renal transplant recipients seen for follow-up in 1978/79 over a 6-month period underwent investigation by micturating cystography. The follow-up period ranged from 4 months to 15 years (mean 3.7 years). Of these,

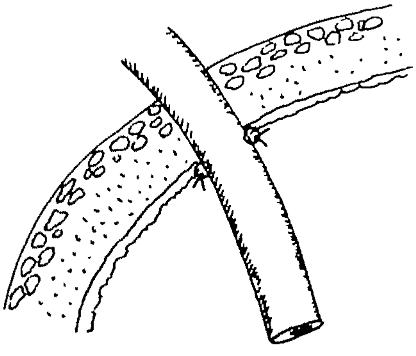

Fig. 1 Tip of transplant ureter protruding into bladder lumen. Free segment should be 1 cm in length.

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49 received kidneys from live related donors and 32 from cadavers. At each visit mid-stream urine specimens were collected and serum creatinine estimations made to check renal function. In addition, patients with recurrent urinary tract infection underwent cystourethroscopy. Patients whose primary renal disease was chronic pyelonephritis with reflux nephropathy and recurrent urinary infections underwent nephroureterectomy, usually at the time of renal transplantation. In all 81 cases the no-tunnel "drop-in" method of ureteroneocystostomy was used.

Operative Technique

After completion of the vascular anastomosis the bladder was distended with 300 ml of sterile 0.9% sodium chloride solution and an 8 cm ventral cystostomy made. With the aid of suitable retractors the posterior bladder wall was brought into view and the closed blades of an artery forceps were passed bluntly through the bladder wall from the mucosal side. The free end of the ureter was then drawn into the bladder, taking care to ensure that the extravesical portion of ureter was under no undue tension and that there was no axial rotation. The ureteric tip was trimmed, so that a 1 cm free segment remained within the bladder lumen. A fine Porges ureteric intubation catheter was then passed as a splint to facilitate subsequent suturing. Four interrupted sutures of 4/0 Dexon were employed to secure the ureteric smooth muscle to the bladder mucosa (Fig. 1). The ureteric catheter was removed and the cystostomy closed in 2 layers. Security of the suture line as well as the implant site was checked by refilling the bladder. A urethral catheter was left to drain the bladder for 10 days.

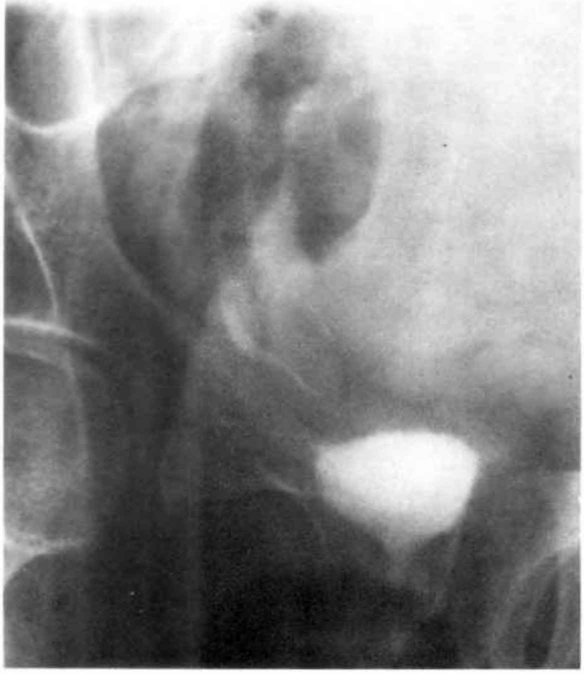

Fig. 2 Patient F.A. Micturating cystogram showing vesicoureteric reflux, Grade I.

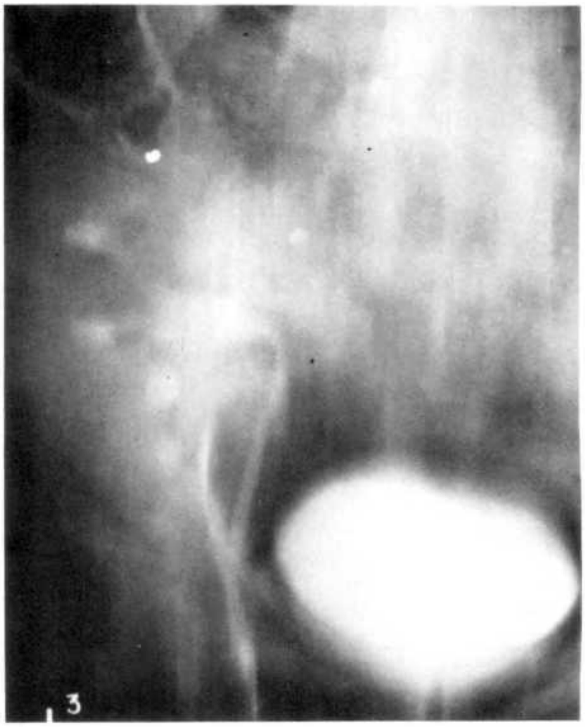

Fig. 3 Patient F.A. IVU showing normal upper urinary tracts.

Results

Of 275 patients who underwent 324 kidney transplants with a no-tunnel "drop-in" ureteric implant between 1961 and 1979, 127 (46%) are alive and well with a functioning graft. Of these, 81 patients were assessed, the remainder residing permanently outside the United Kingdom and/or being followed up by other transplant clinics.

The overall urological complication rate was 10.4% (urinary fistulae in 21 and ureteric obstruction in 13 cases). Three deaths were directly attributed to sepsis due to major urine leaks. Vesicoureteric reflux via the transplant ureter was demonstrated in 6 (7.4%) of the 81 patients. In 5 cases reflux was of a mild grade and present only during voiding (Fig. 2) with no change on serial intravenous urography (Fig. 3). The remaining patient demonstrated Grade IV reflux associated with recurrent urinary infection but was managed conservatively with no deterioration in renal function (Figs. 4 and 5). In all refluxing patients serial intravenous urography has remained normal and the serum creatinine and creatinine clearance did not indicate renal impairment. Recurrent urinary tract infection was present in 29 patients, including the 6 with reflux. In the 52 patients without urinary infection no reflux was demonstrated.

Discussion

Our incidence of vesicoureteric reflux (7.4%) compares favourably with other published series where an antireflux technique has been employed. The incidence of reflux in a series collected from the literature (Debruyne *et al.*, 1978) was 28 out of 227 (12.1%). These results confirm the findings of Rees and Williams (1972), who reported a significant difference in the incidence of reflux between ureteroneocystostomies with and without antireflux mechanisms. Our implant procedure carried no greater frequency of urological complications (10.4%) than other methods currently popular (10% according to Leiter (1975); 9.8% according to Debruyne (1977)).

There is sound experimental evidence in favour of the no-tunnel "drop-in" technique of ureteric implantation (Castro and Fine, 1969). Studies on cadaver bladders indicated that end-to-side mucosa-to-mucosa anastomosis resulted in free reflux. Competence of the vesicoureteric junction was retained if a long free segment of ureter was allowed to protrude into the bladder lumen. Concentric compression of the free segment as the intravesical pressure rises is held to account for the absence of reflux. Interestingly, in 4 of our refluxing patients cystoscopic examination showed the tip of the ureter to be virtually flush with the bladder mucosa.

A number of factors may be responsible for

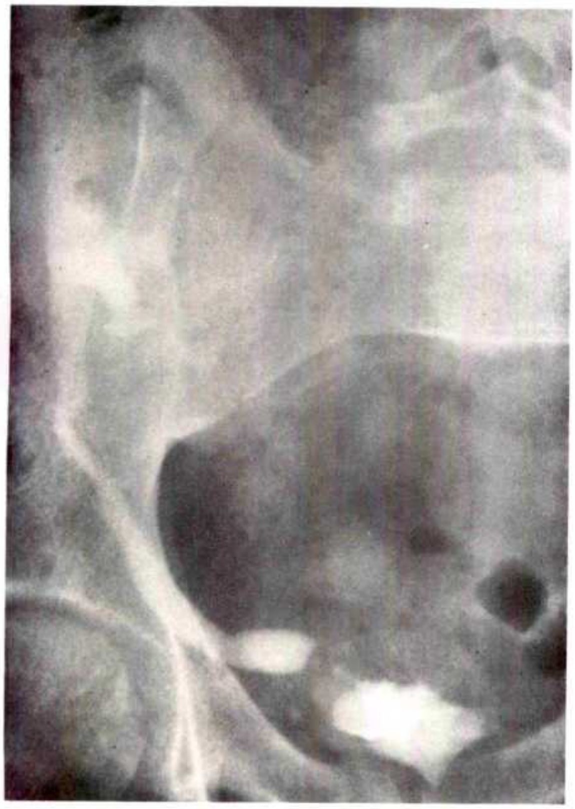

Fig. 4 Patient J.B. Micturating cystogram showing Grade IV reflux.

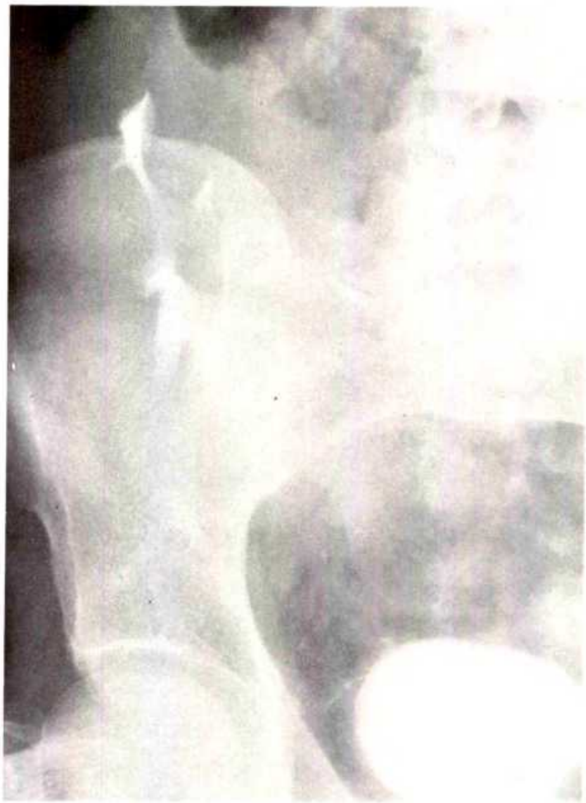

Fig. 5 Patient J.B. IVU showing no upper urinary tract dilatation.

Table The Period of Graft Survival in 6 Patients with Vesicoureteric Reflux with the Donor Source and Warm Ischaemic Times

No.	*Patient*	*Duration of graft (yrs)*	*Donor*	*Warm ischaemic time (min)*	*Reflux grade*
1	S.G.	8	Living	<10	I
2	A.K.	7	Living	<10	I
3	J.B.	5	Cadaver	35	IV
4	F A.	4.5	Cadaver	25	II
5	R H.	3	Cadaver	?	I
6	M.L	2.5	Cadaver	20	I

these failures. All but 2 of our refluxing patients received a cadaver kidney. The ureteric tip may be particularly susceptible to ischaemic fibrosis, although there was wide fluctuation in renal warm ischaemic times (Table). Viability of the ureteric tip may be compromised further by interruption of the vascular supply by one of the 4 anchoring sutures. Rejection of the ureter, causing fibrosis and non-compliance, is yet another factor to be considered. Five out of 6 patients received treatment for repeated rejection episodes.

Doubts have been raised about the importance of vesicoureteric reflux in patients with sterile urine (Debruyne *et al.*, 1978), although others (Yadav *et al.*, 1972) found sufficient evidence to incriminate reflux as the predominant cause of deteriorating allograft function in his patients. In our series, all patients demonstrating reflux had coexistent repeated urinary infection. However, reimplantation was not required in any of the cases and infection was controlled successfully by rotating long-term antimicrobials. Renal damage, whether due to back pressure or lingering infection, may be insidious and close follow-up is advised.

The conclusions based on this study indicate that in the absence of recurrent infection there are no indications for micturating cystography. This technique of ureteroneocystostomy has also been adopted successfully in patients presenting with primary vesicoureteric reflux and small calibre ureter and obstruction or iatrogenic injury of the lower ureter needing reimplantation.

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The Role of N-nitrosamine in Carcinogenesis at the Ureterocolic Anastomosis

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Summary—Seven cases of colonic tumours occurring at the ureterocolic anastomosis (UCA) in patients diverted for benign disease are presented and comparisons made with existing literature.

There appears to be a definite increase in the incidence of colonic malignancy in patients with this diversion. A theory of carcinogenesis involving bacterial activation of endogenously formed N-nitrosamine is suggested. Preliminary results of rectal urine analysis support this theory in that high concentrations of N-nitrosamine have been found and mutagens demonstrated.

In 1851 Lloyd, at St Bartholomew's Hospital, London, first described the use of the ureterocolic fistula in a child with exstrophy. Many ingenious attempts at urinary diversion followed, but it was not until 1911 that the first successful transplant of the ureter into intact colon was performed by Stiles.

The ureterocolic diversion was (and, with the Leadbetter modification, still is) widely used throughout the world. In 1950, Bricker reported the use of the isolated loop of ileum as a urinary conduit. The disappointing long-term results of ureterocolic diversions, coupled with the excellent initial results of the ileal loop, turned most surgeons away from colonic diversions. The ileal loop soon became, and remains today, the diversion of choice for both benign and malignant disease of the lower urinary tract (Fig. 1).

The complications of ureterosigmoidostomies are well known. Despite improved surgical techniques and modern chemotherapy, stricture, hyperchloraemic acidosis and the sequelae of reflux of faecal material into the upper urinary tracts remain major problems.

The first case of carcinoma at the site of the ureterocolic anastomosis was reported by Hammer in 1929 (Fig. 2) but even now, 50 years later, the risk of colon cancer in these patients remains an uncommon hazard. We have studied this particular malignancy in patients diverted for benign disease. Part of this study has been concerned with the analysis of rectal urine in an attempt to identify a possible carcinogen.

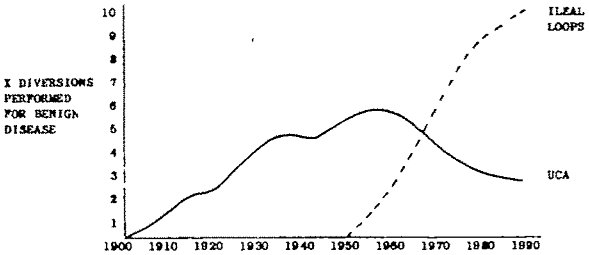

Fig. 1 Relative popularity of ureterocolic and ureteroileal diversions in diagrammatic form (not to scale)

The total dietary nitrate is excreted by the kidneys into the urine. When urine is diverted into the colon it comes into contact with endogenous secondary amine. In the presence of a mixed bacterial flora it has been shown that nitrate plus secondary amine leads to the formation and activation of large amounts of N-nitroso compounds. One of these, N-nitrosamine, is a powerful car-

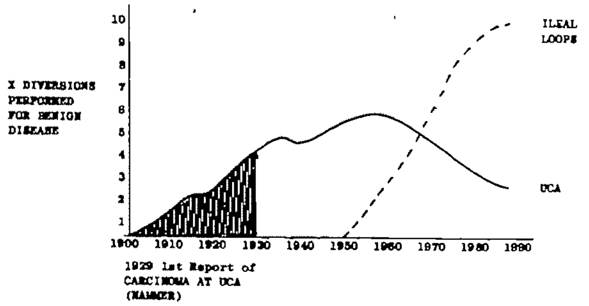

Fig. 2 First case of carcinoma at UCA.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

cinogen to which no laboratory animal has proved resistant. Although there is, as yet, no proof of its carcinogenic action in man, the series of cases presented here suggests that it might, in fact, have such a potential.

Patients and Methods

Three groups of patients, all of whom have undergone ureterocolic diversion for benign disease, have been studied.

Group I	Seven patients with tumour at the anastomotic site treated at the St Peter's Hospitals during the last 30 years. Details of 3 of these cases have been reported previously (Whitaker *et al.*, 1971).
Group II	Fifty-four cases with tumour at the anastomotic site reported in the world literature.
Group III	Eighty-one patients diverted at the St Peter's Hospitals since 1954.

Groups I and II have been analysed with regard to age at tumour diagnosis, latency of the tumour and its histology.

Group III is a prospective survey. The case notes of 81 patients were examined; the patients were then contacted and invited to attend for follow-up examination. Forty-six of the 81 have so far been seen and 29 of these have provided rectal urines for biochemical investigations, including N-nitrosamine assay. The other findings will form the basis of a later publication.

Rectal urine samples were transferred to a protective transport broth and frozen for bacteriological analysis and the remainder of the sample frozen for biochemical analysis. The sample assayed bacteriologically was cultured for total anaerobic bacteria, total aerobes and mean probable number of nitrate-reducing organisms.

Part of the sample for biochemical analysis was assayed for nitrate and nitrite ion concentration. A further part was assayed using a chemiluminescence analyser for N-nitroso compounds and a further portion was filtered through a millipore filter (pore size 0.22 μ) and then assayed for mutagens by the Salmonella mutagenesis assay system (Ames, 1972).

Results

The findings in Groups I and II are summarised in Table 1. Exstrophy was the single commonest antecedent in both groups and, in the majority of cases, diversion was carried out within the first few years of life. In contrast, diversion for other causes (such as incontinence and interstitial cystitis) tended to be carried out in adult life.

In the 61 patients in Groups I and II, the mean latent period between diversion and tumour development was the same (24 years).

Adenocarcinoma was the most common tumour (70% of Group I and 70% of Group II patients). Thirteen (21%) of the 61 tumours were polyps, the majority of which were adenomas, although some were described as reactive and juvenile types.

There was an interesting difference in the latent period according to type of tumour (Table 2) when Groups I and II are considered together; the mean ages at diagnosis of polyps and carcinomas were very similar, whereas the mean latency was strikingly different, being 19.8 years for polyps and 25.8 years for adenocarcinomas.

Table 1 Tumours at Ureterocolic Anastomosis (Benign Antecedents)

		St Peter's cases (Group I)	*Literature review (Group II)*
Antecedent causes	Exstrophy	4	47
	Others	3	7
Age at tumour diagnosis		22-77 yrs (mean 46)	13-70 yrs (mean 32.9)
Latency		15-40 yrs (mean 24.3)	10-50 yrs (mean 24.5)
Histology	Polyp	1	12
	Adenocarcinoma	5	38
	Transitional cell carcinoma	—	1
	Carcinoma of indeterminate origin	1	3

Table 2 Mean Age and Latency of Adenocarcinomata and Polyps Arising at the Ureterocolic Anastomosis

Tumours at ureterocolic anastomosis	*Mean age at diagnosis*	*Mean latency*
Polyps	33.5	19.8
Adenocarcinoma	34.7	25.8

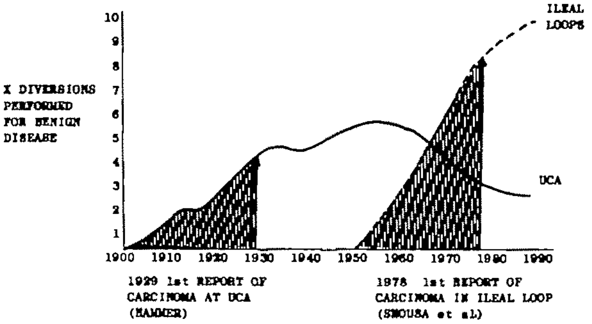

Fig. 3 First case of carcinoma at UCA and first case of carcinoma in ileal loop.

Biochemical Assays in Group III Patients

Assays were complete in 7 of the 29 urines studied and uniformly high levels of nitrate, nitrite and N-nitroso compounds have been found and mutagens demonstrated. In the remaining 22 urines, the presence of mixed bacteria and large amounts of nitrates and nitrites was confirmed and mutagens demonstrated. Given the normal secondary amine production in the colon, N-nitrosamine formation could reasonably be expected.

Discussion

The risk of colonic malignancy complicating ureterocolic diversion has been calculated at between 180 and 7000 times that of the population at large depending on age (Table 3). It is an under-diagnosed malignancy and the clinician should be aware of the high risk group of patients, diverted in the fifties and sixties, who are now in danger.

Analysis of Group I and II cases confirms that this is a malignancy which occurs in the under-50 age group, where colon cancer is rare. The apparent discrepancy between the ages at tumour diagnosis in Groups I and II is probably a reflection of the high percentage of Group I patients who were diverted in adult life.

The constant latency of 24 years before tumour development is reminiscent of that found in industrial bladder cancer, where a carcinogen is known to be active.

Polyps occurring at the ureterocolic anastomosis have a 6-year shorter mean latency than carcinomas. It would not be unreasonable to suggest that, if adenomatous polyps were to undergo malignant change, this process would occur over a period of 5 to 10 years.

The demonstration of N-nitroso compounds in the rectal urine is highly significant, in that these compounds are not normally found, other than in trace amounts, either in human urine or faeces. In fact, N-nitroso compounds have been demonstrated in only 2 other locations in the human body: firstly, in the achlorhydric stomach, when they have been associated with gastric cancer, and secondly, in the mixed urinary tract infection associated with bilharzia when, again, they have been incriminated in local carcinogenesis.

The detection of mutagens in these rectal urines is a further very strong indication that a carcinogen is present.

Because ureterocolic diversions are no longer commonly performed in this country, it may be argued that this tumour is of minor significance. Before accepting this, certain points should be considered.

Firstly, in Third World countries, where external urinary appliances are impracticable or unacceptable, the ureterocolic diversion remains the operation of choice for a great many people.

Secondly, if we accept the likelihood of a powerful, locally active carcinogen at the anastomotic site, it may be that colon loops, currently gaining

Table 3 Estimated Risk of Colon Cancer at the Ureterocolic Anastomosis in Patients Diverted for Benign Disease

Author	*No. of cases followed up*	*No. of cases of carcinoma*	*Incidence per 100,000 population*	*Risk*
Urdaneta *et al.* (1966)	83	3	13,000/100,000	550 × normal population
Parsons *et al.* (1977)	29	2	6900/100,000	280 × normal population
Eraklis and Folkman (1978)	82	4	4.9/100	181 × whole population 7000 × of population aged 25 and under

popularity among paediatric urologists, carry a similar risk of colon cancer.

In 1978 Shousa *et al.* reported an adenocarcinoma at the ureteroileal anastomosis in a patient diverted for exstrophy 20 years prior to the diagnosis of his tumour (Fig. 3). Assuming a latent period similar to that of malignancy occurring at the ureterocolic anastomosis, and the fact that ileal loops have been performed in significant numbers only in the last 20 years, this case may be the warning of many more to come.

Lastly, the recently reported long-term results of ureterosigmoidostomies over the last 30 years, performed with the benefit of better surgical techniques, powerful antibiotics and a clearer understanding of metabolic disturbances, compare favourably with the disappointing long-term results of the ileal loop diversions. It may well be that the wheel may turn full cycle and many urologists will turn their attention back to the colon as a urinary conduit.

We therefore contend that, though rare, carcinoma at the ureterocolic anastomosis is an important malignancy which offers us the chance to identify a human carcinogen and we feel that the question of nitrosamine-induced carcinogenesis requires further study.

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Bladder Exstrophy. Primary Reconstruction with Human Dura Mater

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Summary—A new surgical technique for primary reconstruction of bladder exstrophy is described. Human cranial dura mater is used as an alloplastic free graft to replace the missing anterior bladder wall. The technique has been successfully applied to 8 patients and the early achievement of good bladder capacity seems to improve urinary continence.

Primary reconstruction of the exstrophic bladder has been a challenge to surgeons all over the world. There is little to be found in the literature concerning enlargement of the bladder in cases of exstrophy and statistics concerning post-operative continence are rather discouraging. A good bladder capacity seems to be important in the achievement of continence, however, and some authors have improved their results by selecting only large bladders for primary reconstruction. Continence has been greatly improved by the use of urethral lengthening techniques as proposed by Young (1922) and Leadbetter (1964).

Pigossi (1967) described a method of preservation of homologous dura mater. Dura mater has also been used by Puig (1972), Moraes (1976) and Lima (1977) as artificial cardiac valve material. Based on the work of Kelâmi (1971, 1975) and the experience of one of us (P.P.M.) in replacing the bladder wall with dura mater in cases of tumour, contracted bladder and vesicovaginal fistula, we have used a similar principle in the reconstruction of bladder exstrophy.

Patients and Methods

We have used this technique in 8 cases of bladder exstrophy. The age, sex distribution, follow-up and complications are listed in the Table.

Surgical Technique

The basic principles of technique are similar to those used by other authors (Figs. 1-4). Young's method of urethral lengthening has been used. The whole dome of the bladder is completed with dura mater which is anchored to the remaining bladder wall with a 2-layer suture of polyglycolic acid. Efforts should be made to ensure a watertight closure. The bladder is drained suprapubically and an 8 or 10 FG urethral catheter is left indwelling for 10 days. The suprapubic drain is removed around the twentieth post-operative day.

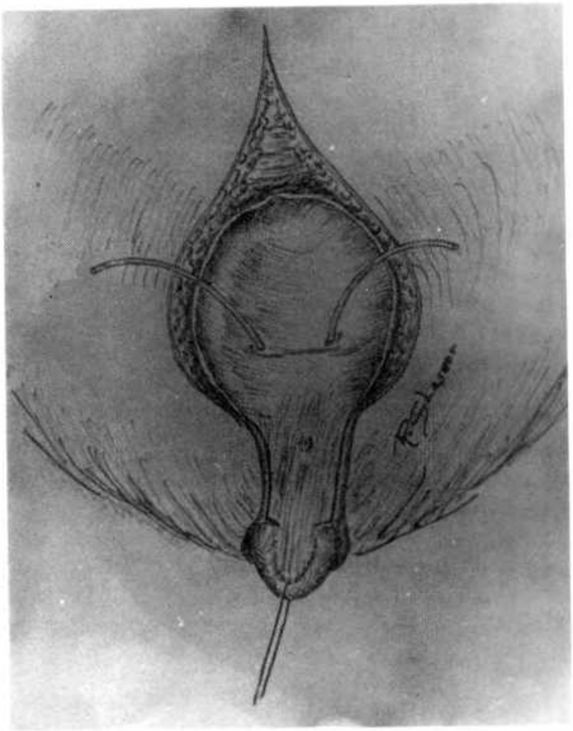

Fig. 1 Bladder and urethra are separated at the mucocutaneous line. Ureters are catheterised to facilitate dissection.

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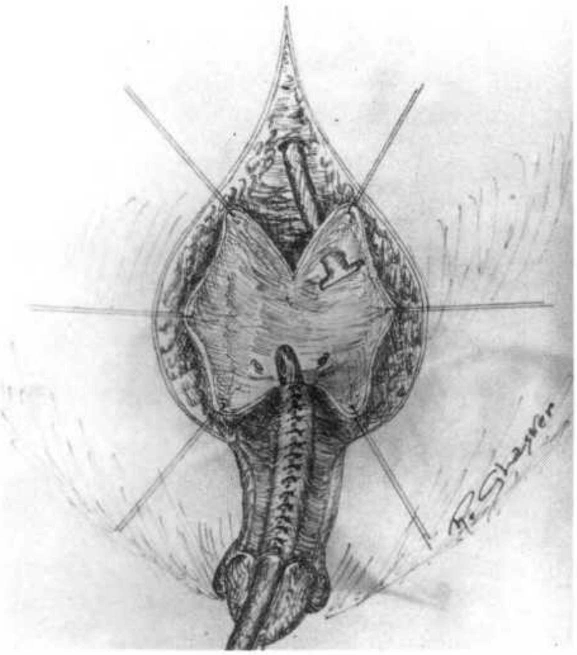

Fig. 2 Urethral reconstruction has been completed, including the lengthening procedure. Bladder wall is split to facilitate anchoring the dura.

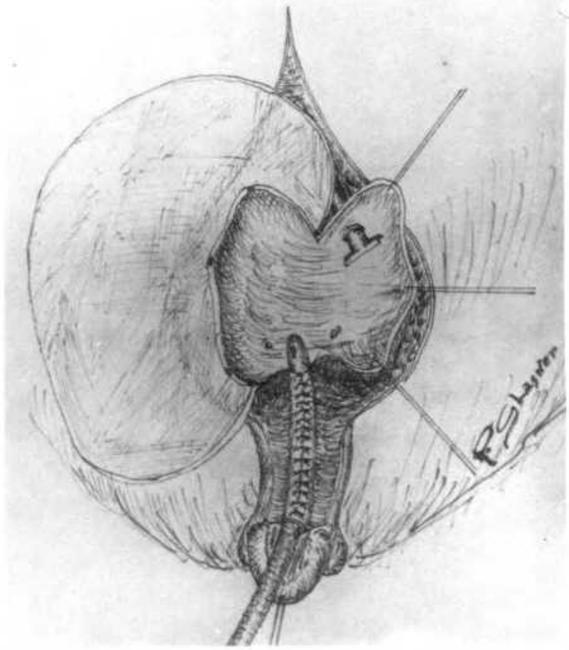

Fig. 3 The first anchoring suture is shown. Note the suprapubic tube through the bladder wall.

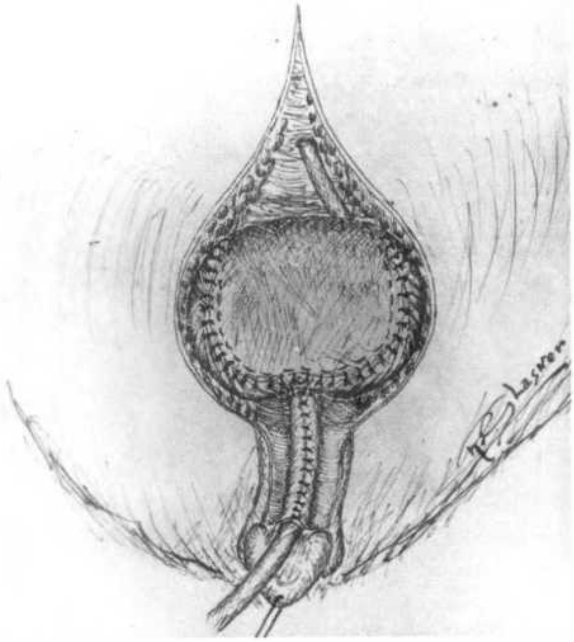

Fig. 4 The dura mater is completely anchored to the bladder wall.

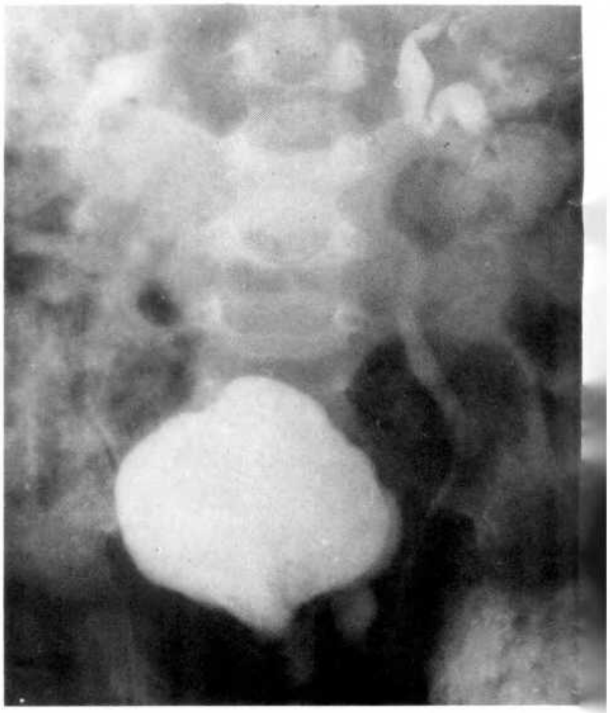

Fig. 5 Case 1. Excretion urogram one month post-operatively. A 90-min film showing a well shaped bladder.

Table

Case no.	*Age*	*Sex*	*Follow-up in months*	*Result*	*Complications*
1	18 months	F	21	Good	—
2	17 months	F	21	Good	—
3	2 years	F	20	Good	Bladder stone
4	4 years	M	20	Good	Reflux
5	3 months	M	19	Incontinent	Dehiscence of urethral suture
6	4 months	M	17	Incontinent	Dehiscence of urethral suture
7	9 years	F	14	Partial incontinence	Reflux, hydronephrosis
8	7 years	M	12	Undiversion. Continence improving	—

Bilateral iliac osteotomies are performed in the same session and the pubic rami are kept together using a 2/0 polypropylene suture. Immobilisation is ensured by bandaging the legs together in internal rotation. The bandages are removed after 6 to 8 weeks. Antibiotics are used routinely in the post-operative period and a combination of ampicillin and gentamicin has been our choice.

Results

All patients achieved some degree of urinary continence from the day the suprapubic tube was removed. Patients 1, 2 and 3 had dry periods lasting up to 2 h in the early post-operative months (Fig. 5).

Case 3 became incontinent after 5 months and complained of abdominal pain. X-ray showed 2 stones in the bladder and cystolithotomy was performed. Crystallographic analysis of the stones showed calcium oxalate. Culture of the matrix produced no growth, although the urine culture had been positive for *Proteus*. At follow-up after 20 months the girl has a good bladder capacity and is continent (Fig. 6).

Case 4 had difficulty in distinguishing bladder and rectal sensation and this required some training. At follow-up 6 months later he was partially incontinent. The cystogram showed a well shaped bladder but there was bilateral vesicoureteric reflux. Since there was upper tract deterioration he underwent an anti-reflux procedure. Macroscopically there was no difference between the dome, where the dura mater was implanted, and the lateral wall of the bladder. Four specimens were taken for biopsy and microscopy showed smooth muscle bands in each. The boy now has a normal upper tract and can remain dry for periods of one hour (Fig. 7).

Cases 5 and 6 are now incontinent, although they appeared to have dry periods in the early post-operative months. Case 5 had a second duraplasty one year after the original operation because his bladder was still very small and there was

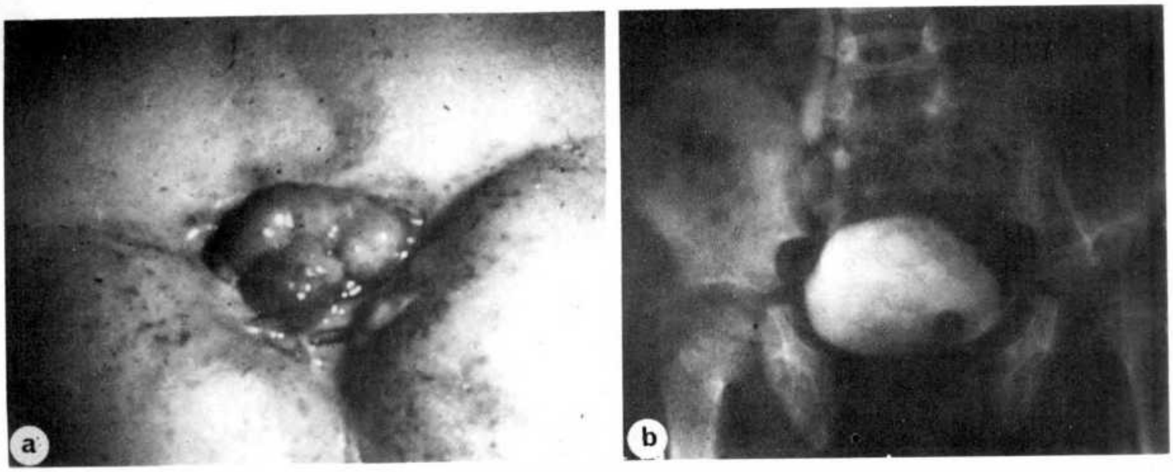

Fig. 6 Case 3. (a) Small bladder with marked inflammatory changes. (b) Excretion urogram: 40-min film 20 months after reconstruction.

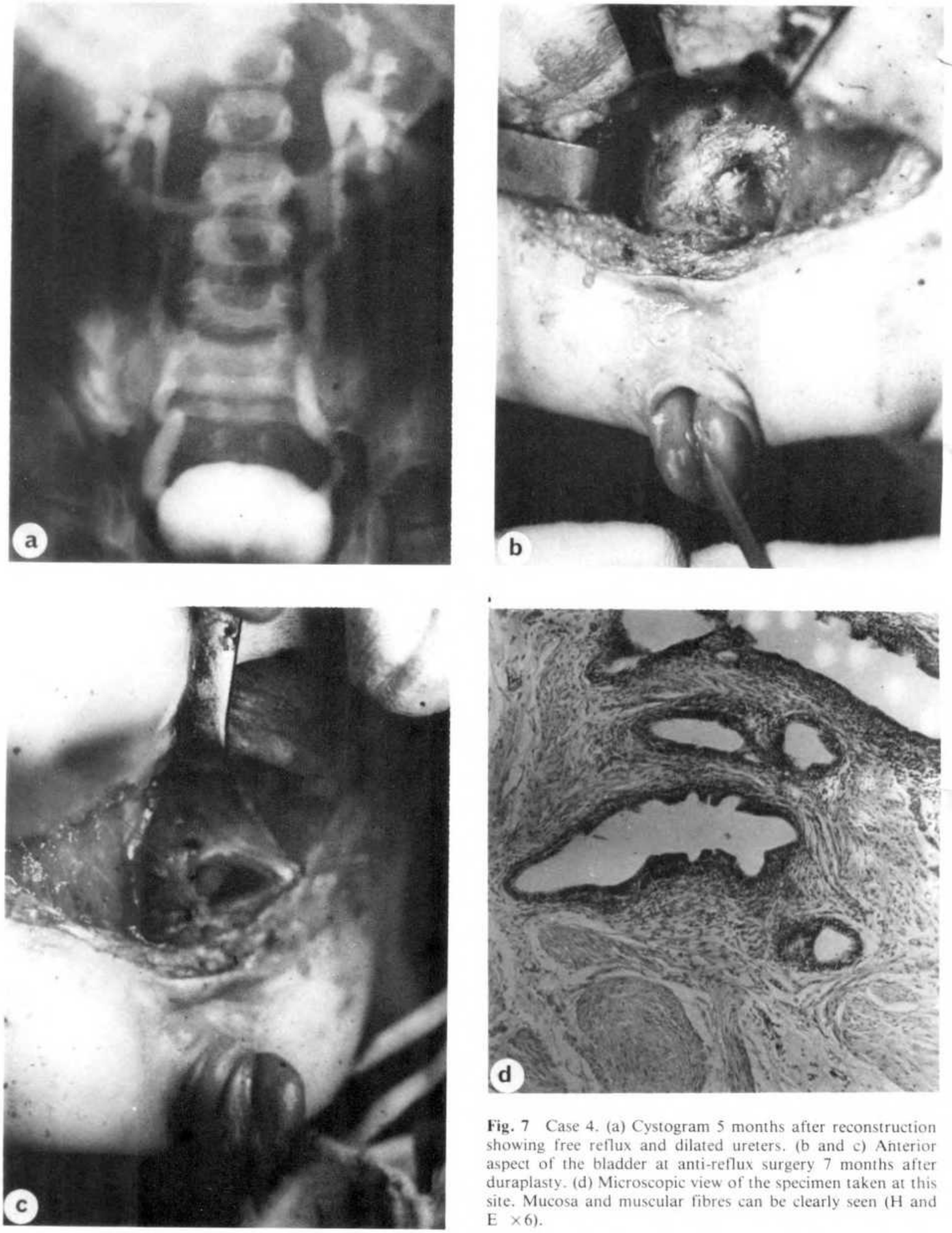

Fig. 7 Case 4. (a) Cystogram 5 months after reconstruction showing free reflux and dilated ureters. (b and c) Anterior aspect of the bladder at anti-reflux surgery 7 months after duraplasty. (d) Microscopic view of the specimen taken at this site. Mucosa and muscular fibres can be clearly seen (H and E ×6).

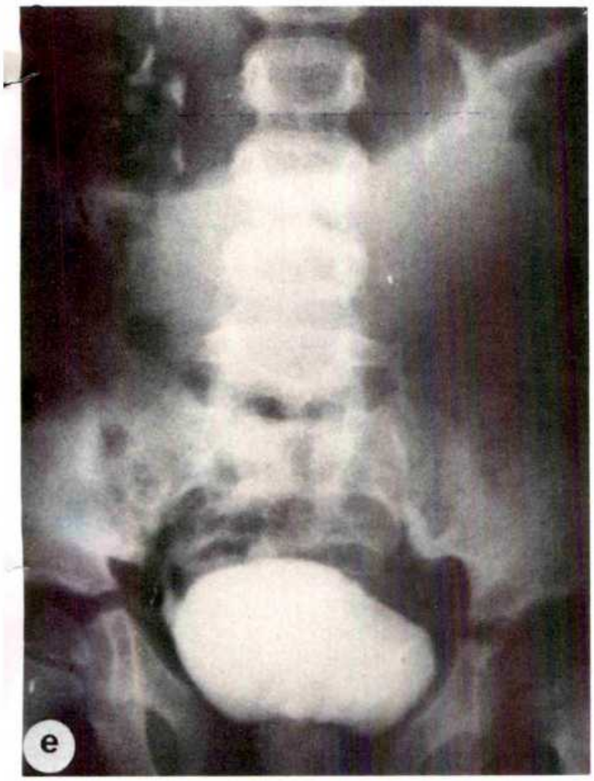

Fig. 7—*continued.* (e) Excretion urogram 6 months after anti-reflux surgery.

complete dehiscence of the urethra and bladder neck.

Case 6 had disruption of the bone suture, and dehiscence of the lower part of the wound occurred on the tenth post-operative day. During re-exploration the dura mater was inspected and some disruption was observed and sutured. The dura mater seemed very thin and soft. There was some post-operative leakage of urine which resolved spontaneously. He is now incontinent and is being considered for a second urethral reconstruction.

Case 7 showed marked dilatation of the upper tracts 6 months after reconstruction. Cystography showed free ureteric reflux and the ureters were reimplanted. At follow-up one year later excretion urography showed further dilatation on the right side and some improvement on the left. The cystogram showed no reflux. She is partially incontinent.

Case 8 had an ileal loop diversion in the neonatal period after failure of an anatomical reconstruction performed elsewhere. The bladder had been left in place. Reconstruction was performed by our technique and an undiversion with a second dura patch was carried out 7 months later. There were no complications and the radiological appearance 4 months following undiversion was good. He is able to remain dry for 30 to 40 min (Fig. 8).

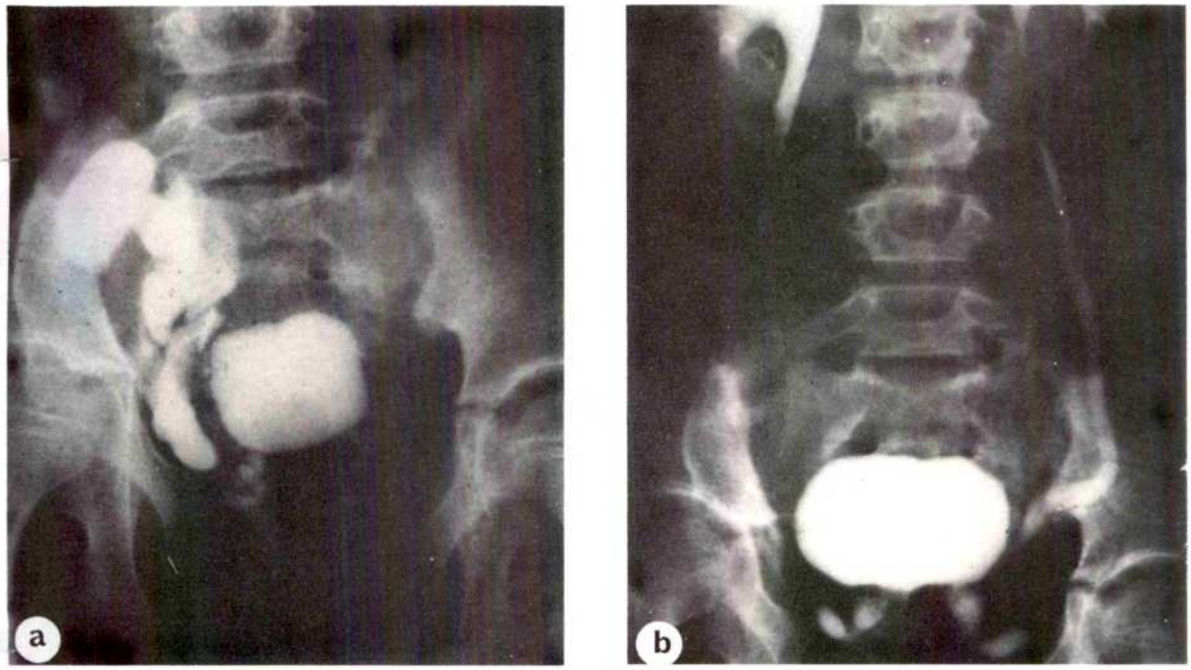

Fig. 8 Case 8. (a) Loopogram and cystogram 7 months after reconstruction. (b) Excretion urogram 4 months after undiversion. Note original ureteric stumps.

Discussion

Although in this series the exstrophic bladders were small, the results seem as good as those in other series where rigid criteria for reconstruction in respect of an adequate bladder capacity were adopted (Williams, 1972; Jeffs, 1978). The complications which occurred in our series are similar to those previously published by other workers and cannot be related to the use of dura mater. Our results strongly suggest that dura mater can, with advantage, be used routinely in every case of exstrophy even when there is a large bladder. It can also be used in cases of exstrophy where reconstruction has already been carried out and where the capacity is small.

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Biofeedback Treatment of Intermittent Urinary Retention

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Summary—The treatment of a 29-year-old woman with intermittent urinary retention using biofeedback is described and discussed in the context of the pathophysiology of reflux urethral instability and related disorders of micturition. During attempts to train the patient to raise the pitch of an auditory biofeedback signal, which varied directly with intrinsic bladder pressure, evidence appeared for the involvement of sensory neuronal pathways in the disorder. This and other evidence are incorporated within an explanatory hypothesis.

Involuntary retention of urine in the absence of any detectable organic abnormality is well documented (Larson *et al.*, 1963; Nesbitt *et al.*, 1965; Barrett, 1976). McGuire (1978) has suggested that abnormal bladder dilatation caused by involuntary retention of urine may be followed by a reduction of sensory perception of bladder activity. This may result in what McGuire has termed reflex urethral instability, characterised by incontinence and large post-voiding residual urine volumes. In some cases, incontinence occurred intermittently against a background of persisting urinary retention, and the following case showed such a pattern. It is presented and discussed with the aim of modifying McGuire's hypothesis, and of suggesting a new treatment approach for a troublesome and refractory condition.

Patient and Method

B.R., aged 29, white, single, had suffered from post-operative retention of urine following her second termination of pregnancy 11 months before referral to the author for psychiatric assessment. The retention had persisted in spite of appropriate drug treatment and an organic basis had been excluded by detailed urological investigations, after which she was taught self-catheterisation. This she had been performing 1 to 3 times a week for 9 months. Every 2 to 3 weeks, her retention was replaced for 1 to 3 days by severe urgency and frequency, when she involuntarily passed small amounts of urine at least 15 times a day, and during which time her urine was not usually infected.

After psychiatric assessment, fortnightly sessions of individual psychotherapy were conducted for 5 months, with the patient reporting no change in bladder function throughout and insisting that she had no desire to change as a person. She was then given 11 one-hour sessions of biofeedback training over a period of 15 weeks, with the aim of increasing detrusor activity and of restoring normal voluntary inhibition of the detrusor reflex.

Apparatus

A 14-gauge urethral catheter was used for filling the bladder with 0.9% saline, pre-warmed to body temperature. A 1 mm fluid-filled catheter, placed inside the urethral catheter, measured total bladder pressure. A 2 mm fluid-filled catheter, protected from blockage by a finger stall, was introduced into the rectum to measure rectal pressure, which closely approximates to the pressure within the abdomen. Subtraction of the intra-abdominal pressure from the total bladder pressure yields the intrinsic bladder pressure. Since intrinsic bladder pressure is determined by the activity of the bladder itself, it is the measure used for biofeedback, and was obtained by attaching the fluid-filled catheters from bladder and rectum to a differential transducer, as shown in the Figure. The signals from the differential transducer are amplified and fed into a chart recorder, which allows the option of visual feedback through a mirror for patients who find this helpful. The present patient preferred auditory feedback (see Fig.). The

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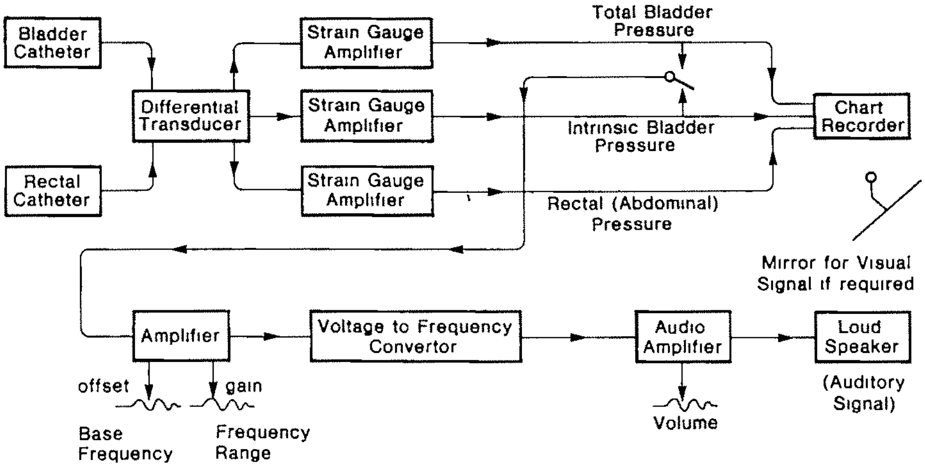

Fig.

auditory signal from the loudspeaker is adjusted to obtain a baseline pitch for each session, which then rises and falls in relation to rises and falls in intrinsic bladder pressure.

Procedure and Results

During each biofeedback session the patient was encouraged to try to raise the pitch of the auditory signal after a measured amount of 0.9% saline had been passed into her previously emptied bladder. Any rise in the pitch of the signal indicated active movement of the detrusor muscle. Throughout the 15 weeks of treatment the patient kept a detailed record of the frequency of self-catheterisation and of any spontaneous voiding of urine, together with the volumes obtained.

At the start of the first 3 sessions an average of 980 ml was removed from the patient's bladder, indicating abnormal distension. The patient was unable during the first 3 sessions to increase the pitch of the auditory signal, even though over 800 ml of saline were passed slowly into her bladder on each occasion. She reported a complete absence of bladder sensation. During the third session an unexpected observation was made: the patient had mild diarrhoea and her gut was unusually motile; when contractile movement of the bowel occurred, the patient reported her bladder as contracting. On each occasion, however, intrinsic bladder pressure was unchanged. The patient presumably interpreted contraction of the gut adjacent to the bladder as movement of the bladder itself. Sessions 4 and 5 were therefore devoted to teaching the subject to discriminate between bowel activity and bladder activity and sensation, and during the sixth session the patient was for the first time able voluntarily to raise the pitch of the auditory signal, after 750 ml of saline had been slowly infused into her bladder.

Up to this time the patient's records showed no change in bladder activity, but the day after the sixth session she began to void voluntarily once a day in the mornings. This was the first time she had been able to void voluntarily since her urinary retention began 20 months previously. It is of note that she had complained of considerable discomfort and some pain in the bladder area after the fourth and fifth sessions, which may have been an aspect of the early phase of the restoration of sensory perception.

The volume of urine removed from the patient's bladder at the start of each session fell from 830 ml at the sixth session to 510 ml at the eleventh. The volume of saline required before a bladder contraction occurred fell from 750 ml at the sixth session to 370 ml at the eleventh, and the volume of urine voluntarily voided in the mornings averaged approximately 300 ml in the week after the eleventh session, when the patient also became able to void an average of 150 ml in the evenings. Two weeks after the eleventh session self-catheterisation ceased to be necessary, and at the 6-month follow-up the patient described her micturition as having been entirely satisfactory for at least 3 months.

Discussion

McGuire (1978) has suggested that the deficit in patients showing a clinical pattern similar or identical to the case described is a sensory one. He proposes that the abnormal dilatation of the bladder during involuntary retention may selectively damage the sensory neuronal network in the bladder wall. This prevents normal cerebral perception of bladder activity, so that patients are unaware of events preceding the reflex-determined voiding process. Their first embarrassing awareness of urine loss occurs only as their urine leaks away. A central feature of McGuire's hypothesis is the experimentally based suggestion that motor and sensory nervous pathways to and from the bladder travel by separate routes (Bradley *et al.*, 1976), so that damage to the sensory neuronal network can occur without disruption of the motor pathways.

McGuire's attractive and imaginative hypothesis fails, however, to accommodate the following points. First, it is not easy to understand why neuronal damage resulting from overdistension of the bladder should selectively affect sensory pathways. Second, deliberate bladder overdistension is not uncommonly used as a treatment for urinary incontinence associated with detrusor instability, and there have been no reports of the initiation or exacerbation of reflex urethral instability after the procedure. Pengelly *et al.* (1978) distended the bladders of 46 patients with urinary incontinence, using distension volumes of up to 1600 ml, and found little or no subsequent change in bladder activity. Third, if the lesion in reflex urethral instability is one of fine neuronal networks, it would not be unreasonable to expect gradual recovery in a proportion of cases. This occurred in none of McGuire's reported cases, most of which required long-term and continuing management with drugs and intermittent catheterisation.

The following modification of McGuire's hypothesis aims to accommodate the above points.

Although psychogenic urinary retention is a well-established clinical entity, and psychogenic factors are increasingly being recognised as important in the unstable bladder (Hafner *et al.*, 1977; Frewen, 1978), the neuronal pathways involved remain to be established. The recent evidence of separate motor and sensory pathways between the brain and the bladder (Bradley *et al.*, 1976) permits the hypothesis that the sensory pathway may be suppressed or inhibited by those cerebral cortical mechanisms which operate during the process of psychological dissociation which is central to psychogenic disorders of bodily function. It is proposed, then, that the sensory defect in reflex urethral instability is often a psychogenic one, based on the psychologically determined dissociation from consciousness of aspects of sensory input to the cerebral cortex from the bladder.

An explanation for the occurrence in this syndrome of a shift from urinary retention to incontinence, and sometimes back again, is suggested by the work of Fall (1978), who found evidence for 2 separate reflex systems governing micturition, one operating at high intravesical pressures and the other at low ones. It may be that psychogenic retention of urine is initiated by a protective, psychologically determined dissociation from consciousness of painful sensory input from an overdistended bladder. This suppression of sensory cortical input might interrupt the function of the micturition reflex operating at high intravesical pressures. More precisely, the absence or reduction of sensory cortical input might prevent the occurrence of an efferent voluntary motor cortical discharge releasing bladder inhibition. Presumably the low pressure circuit would not be affected, and would therefore permit the pattern of bladder emptying seen in reflex urethral instability (and also in detrusor instability); this pattern of emptying seems compatible with the nature of the proposed low pressure circuit.

In the case reported, biofeedback presumably reactivated the proposed high pressure circuit: it will be recalled that over 800 ml of saline were introduced into the bladder in the early stage of biofeedback treatment, placing bladder activity within the range of such a high pressure circuit.

Given the poor response of reflex urethral instability to conventional therapies and the negligible risk attached to biofeedback procedures, further research on the application of biofeedback to this and related disorders seems justifiable. Cardozo *et al.* (1978) have had encouraging results using an almost identical biofeedback technique with detrusor instability.

It is not always easy for urologists and others involved in the treatment of distressing bladder disorders to incorporate psychological concepts such as dissociation in their thinking about underlying pathophysiology, and it is not often that psychiatrists and others familiar with psychological concepts join them in the front line of clinical work. It seems likely, however, that real progress in the understanding and treatment of these

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Different Cystometric Types of Deficient Micturition Reflex Control in Female Urinary Incontinence with Special Reference to the Effect of Parasympatholytic Treatment

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Summary—The effect of 4 weeks' treatment with emepronium bromide in 20 incontinent female patients with detrusor hyperreflexia was compared to the effect in 20 patients who did not have uninhibited detrusor contractions during filling cystometry but who were unable to suppress a voluntarily induced detrusor contraction.

In both groups, 65% benefited from the drug and no statistically significant differences were seen in the decrease in frequency of voiding and incontinence episodes during treatment. There were no differences between the groups for age, type and degree of urinary incontinence, and radiological findings of bladder suspension defects.

In these patients it is important to perform cystometry, including detrusor reflex activation procedures and the testing of their ability to suppress a voluntarily induced detrusor contraction.

Rapid fill cystometry, including detrusor reflex activation procedures in female patients with urinary incontinence, has revealed a high incidence of detrusor hyperreflexia—71% and 55% (Arnold, 1974; Nordling *et al.*, 1979).

Detrusor hyperreflexia has been defined as the presence of contractions during cystometry exceeding 15 cm of water when the patient has been asked to inhibit voiding (International Continence Society, 1976). In a previous study of 100 consecutive incontinent female patients referred for urodynamic evaluation, we found detrusor hyperreflexia in 42% according to this definition. A further 13% were regarded as having detrusor hyperreflexia in that they were unable to suppress a voluntarily induced detrusor contraction once it had started. Preliminary results suggested that parasympatholytic treatment was as effective in the latter type of detrusor hyperreflexia as in the former (Nordling *et al.*, 1979).

Emepronium bromide (Cetiprin) has proved to be an effective drug in the treatment of patients with urge incontinence and detrusor hyperreflexia (Brocklehurst *et al.*, 1972; Hebjørn and Walter, 1978). This study was undertaken to compare the effect of treatment with emepronium bromide in incontinent female patients with both types of detrusor hyperreflexia.

Patients and Methods*

The mean age and range for the 20 patients in each group were 49.4 years (32-65 years) and 47.7 years (29-72 years) respectively. The findings at colpocystourethrography were not significantly different for Type 1 and Type 2 detrusor hyperreflexia (Table 1). Five and 6 patients in the 2

Table 1 Findings at Colpocystourethrography in 40 Incontinent Female Patients Classified According to Olesen and Walter (1977)

	Type 1	*Type 2*
Anterior suspension defect	6	7
Posterior suspension defect	7	4
Mixed suspension defect	3	1
Hyperactive bladder	0	2
Normal	4	6

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* Methods, definitions, and units conform to the standards proposed by the International Continence Society except where specifically noted.

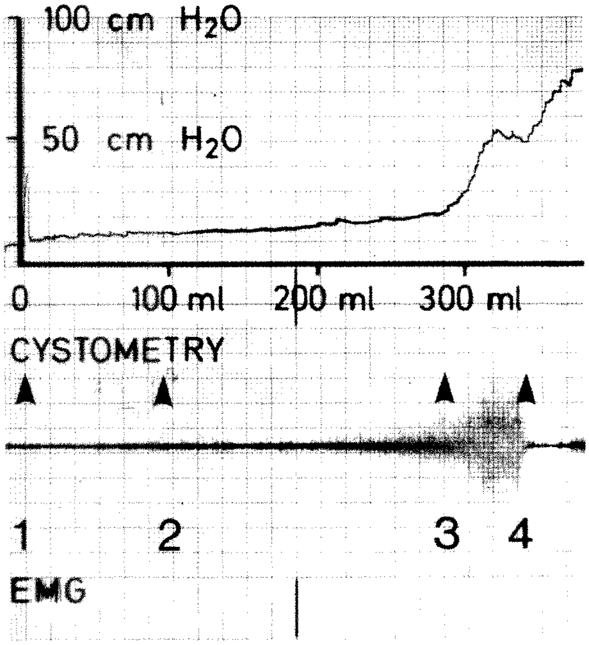

Fig. 1 Detrusor hyperreflexia Type 1. (1) Start of bladder filling; the patient is instructed to suppress micturition. (2) First sensation of fullness. (3) Uninhibited detrusor contraction begins. (4) Instruction to void. The patient is able to relax sphincter activity during detrusor contraction.

groups respectively had previously undergone operation for urinary incontinence. Ten patients had had vaginal repairs and one a urethrosuspension operation. Five patients in each group had pure urge incontinence, 6 and 8 respectively pure stress incontinence, while the rest claimed to have both stress and urge incontinence.

A further 3 patients in each group had to discontinue treatment within 4 weeks because of side effects and these patients were included only in the evaluation of side effects.

Cystometry was performed with CO_2 as the filling medium at a continuous rate of 200 ml per min through a transurethral 16 FG Foley catheter using the DISA CO_2 cystometer, type 21 G O 1. Cystometry was performed with the patient in the supine as well as the standing position. The patient was instructed to inhibit micturition during bladder filling. When the patient felt discomfort or pain the CO_2 flow was stopped and the patient was asked to cough. After coughing the patient was asked to void without straining. If a detrusor contraction above 15 cm of water could be elicited, the patient was again instructed to suppress micturition. From our experience, a patient with intact detrusor control will normally be able to

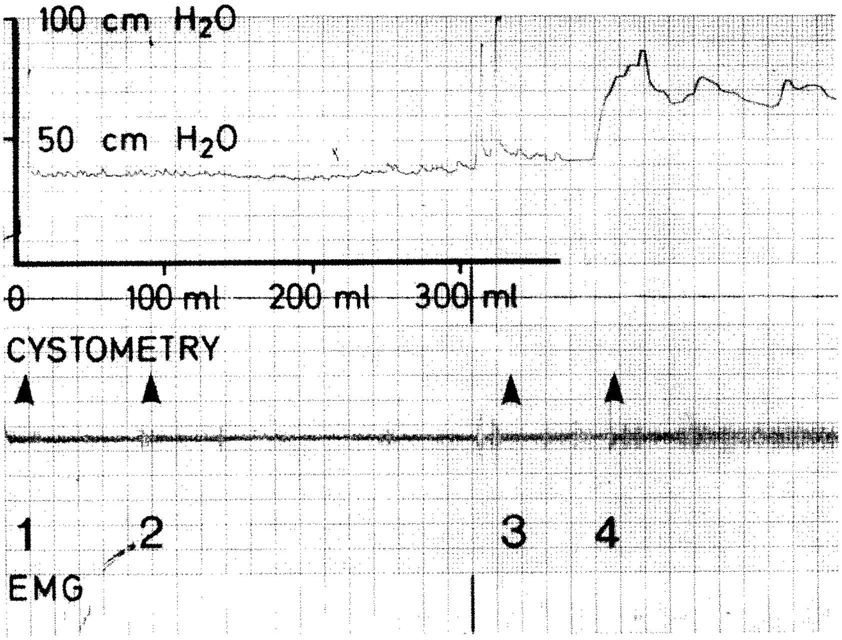

Fig. 2 Detrusor hyperreflexia Type 2. (1) Start of bladder filling. (2) First sensation of fullness. (3) Coughing followed by cessation of bladder filling. The patient is then asked to void. (4) Patient asked to inhibit voiding, but is unable to suppress detrusor contraction to pre-voiding level within 50 s.

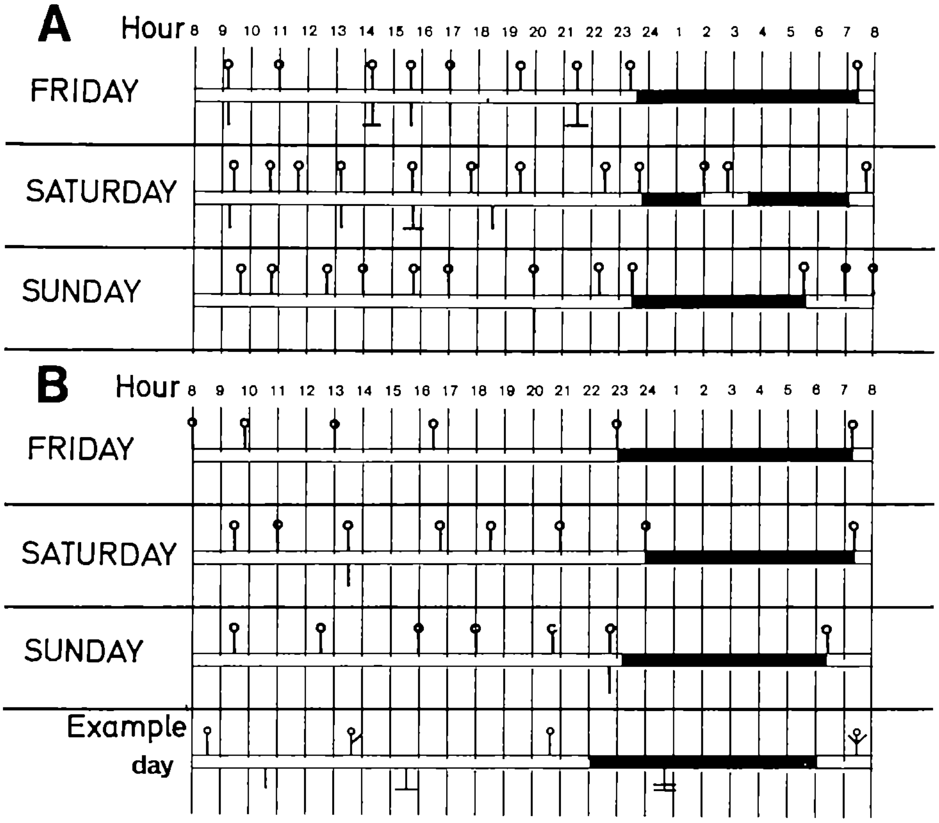

Fig. 3 Micturition chart for registration of voiding events during a 3-day period. ⫯ = Normal voiding. ⟟ = Dysuria. ⚲ = Severe pain during voiding. | = Incontinence episode. ⊥ = Change of underwear. ⫫ = Severe incontinence episode. ■ = Sleep period. A is the registration before, and B after 4 weeks' treatment with Cetiprin 200 mg qid.

suppress the contraction, thus decreasing the intravesical pressure to the pre-voiding level within 50 s.

Patients with uninhibited detrusor contractions during bladder filling or after coughing in the supine and/or standing position have been classified as detrusor hyperreflexia Type 1 (Fig. 1), and patients without uninhibited detrusor contractions but unable to suppress a voluntarily induced detrusor contraction within 50 s as detrusor hyperreflexia Type 2 (Fig. 2) (Nordling *et al.*, 1979).

Assessment also included vaginal examination and colpocystourethrography in the straight lateral projection (Olesen and Walter, 1977).

For comparison of the effect of parasympatholytic treatment 20 consecutive patients in each cystometric group fulfilling the following criteria entered the study. The symptom—urinary incontinence—should be present without urinary infection and with no overt sign of neurological disease. At cystometry residual urine should be less than 50 ml. The patients should be without local discomfort due to genital prolapse, and complete 4 weeks of treatment with emepronium bromide 200 mg qid. No other parasympatholytics were given during the study.

The effect of treatment was evaluated subjectively after one month. To obtain an objective assessment, each patient completed a 3-day micturition chart (Friday to Sunday) the week before treatment and on the same 3 days during each of the 4 weeks of treatment (Fig. 3). Control cystometry was not carried out, since treatment with emepronium bromide has shown no effect on cystometric findings (Hebjørn and Walter, 1978).

To compare the serum levels of emepronium bromide (Vessman *et al.*, 1970), a blood sample was obtained after 4 weeks of treatment before the morning dose of the drug was taken, *i.e.* 8 to 10 h after the last drug intake. To estimate the total drug intake, all emepronium bromide tablets left over at the end of the study were counted.

Table 2 Subjective Evaluation of the Effect of Treatment

Effect	*Type 1*	*Type 2*
Satisfactory	9	4
Unsatisfactory	4	9
No effect	7	7

Patients were instructed to drink a glass of water after each tablet to avoid oesophagitis due to local irritation (Kavin, 1977).

Results

No significant differences were seen in the patients' evaluation of the effect of the drug (Table 2). In both groups 65% (95% confidence limits 41-85%) reported a beneficial effect.

From each micturition chart the mean daily number of voidings and episodes of incontinence were calculated (Table 3).

Fifty-five per cent of patients with Type 1 and 80% of patients with Type 2 detrusor hyperreflexia had a decrease in the number of voidings and 75% and 55% respectively a decrease in the number of incontinence episodes after completion of treatment.

No significant differences in the frequency of voiding and incontinence episodes were seen in the 2 groups before treatment, nor were there any significant differences in the decrease in frequency of voiding and incontinence episodes during treatment ($P > 0.1$, Mann-Whitney rank sum test).

Table 3 Frequency of Micturition and Incontinence Events 24 h 7 before and 2 during the 4 Weeks of Treatment

		Voidings median (range)	*Incontinence episodes median (range)*
	Before treatment	9.5 (4.7-22.7)	1.0 (0-6.7)
	Week 1	8.4 (4.3-13.0)	0.7 (0-5.0)
Type 1	Week 2	8.7 (4.0-15.3)	1.0 (0-6.3)
	Week 3	7.7 (4.3-12.0)	0.7 (0-5.0)
	Week 4	8.3 (4.7-13.7)	0.5 (0-4.0)
	Before treatment	8.7 (5.3-15.0)	1.2 (0-6.7)
	Week 1	7.7 (4.0-12.7)	0.7 (0-4.3)
Type 2	Week 2	7.7 (4.0-11.3)	0.3 (0-4.7)
	Week 3	7.9 (4.0-11.7)	0.5 (0-4.7)
	Week 4	7.7 (4.0-12.0)	0.7 (0-5.7)

Table 4 Number of Tablets Left Over and Concentration of Emepronium Bromide after 4 Weeks of Treatment

	Type 1	*Type 2*
Number of tablets Median (range) (Expected 14)	17 (10-39)	19 (8-42)
Emepronium bromide Serum conc. μg/l Median (range)	24 (7-62)	24 (3-152)

Serum concentration of emepronium bromide and the number of tablets left over at the end of the study were comparable for both groups (Table 4).

Analysis of all patients who described the effect of treatment as satisfactory showed a significant ($P < 0.05$) decrease in the number of voidings as well as in the number of incontinence episodes. This did not apply to patients unaffected by the drug ($P > 0.1$, Wilcoxon matched pairs signed rank test). However, the presence or absence of a bladder suspension defect and the serum level of emepronium bromide were not significantly different for patients who assessed their treatment as satisfactory or as ineffective. In addition, the daily frequency of voiding and incontinence episodes before treatment was not significantly different for these groups.

The side effects of treatment are shown in Table 5. Only 10 of 46 patients had no side effects at all.

Discussion

Patients with both types of detrusor hyperreflexia

Table 5 Side Effects during Treatment, as Indicated on Request and Shown as Percentage of the 46 Patients

	Week			
	1	*2*	*3*	*4*
Headache	2	2	4	4
Dizziness	4	2	4	7
Visual disturbances*	7	7	4	7
Dry mouth*	28	30	33	33
Nausea, heartburn*	17	13	15	22
Constipation	2	9	9	9
Incomplete bladder emptying	0	2	2	2
Oedema*	4	0	0	0
Exanthema*	1	0	0	0

* Side effects for 6 patients who had to discontinue treatment.

responded equally well to parasympatholytic treatment. Its placebo effect (Brocklehurst *et al.*, 1972) should be the same for all patients, since they were treated simultaneously by the same doctors and the effects of the treatment were registered on micturition charts completed by the patients themselves. In terms of age, radiological findings, type of incontinence, daily frequency of micturition and incontinence episodes and serum level of emepronium bromide, there was no significant difference between the 2 groups. Based on these findings, the significance of a Type 2 detrusor hyperreflexia in female incontinence is quite as important as "the ordinary" Type 1. In these patients, cystometry should therefore include detrusor reflex activation procedures as well as testing of their ability to suppress a voluntarily induced detrusor contraction.

Unfortunately, not all patients were cured with emepronium bromide 200 mg qid. An increased dose, *e.g.* 400 mg tid, has been of value in some cases and the use of micturition charts helps to assess its effects. Results show that treatment for only one or 2 weeks is usually enough to indicate its effectiveness. Assessment of the pre-dose serum level of the drug is of little prognostic value, since good as well as poor results were seen with the same serum levels. Furthermore, the number of voidings and incontinence episodes and the findings at voiding cystourethrography are of no prognostic value.

In addition to detrusor hyperreflexia, most patients in this study had a bladder suspension defect, and about one-third claimed to have pure stress incontinence. The bladder suspension defect itself may be responsible for some stress incontinence in these patients after parasympatholytic treatment, but the question of whether operative treatment is preferable to medical treatment in a patient with a bladder suspension defect and either type of detrusor hyperreflexia remains unanswered.

Not all of the side effects noted in this study were necessarily due to emepronium bromide and the system of direct inquiry may be responsible for the high figures. In fact, most side effects were mild and caused only 13% of the patients to discontinue treatment.

Acknowledgements

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Elastin and Collagen in the Normal and Obstructed Urinary Bladder

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Summary—Histological and chemical studies were carried out on the elastin and collagen content of the normal and the obstructed urinary bladder wall. The observations were made on 3 different age groups: (1) 3-month-old children with vesical outlet obstruction, (2) children aged between 4 and 8 years with partial vesical obstruction, and (3) adults with a chronically obstructed bladder.

An increase in elastic tissue was shown only in the newborn and in the adults. The collagen did not vary in any of the cases studied. The elastin showed an increase in polar amino acids in the pathological organs compared with the normal. A similar increase in elastin was observed in normal individuals as a result of the ageing process.

It is known that vesical outlet obstruction produces functional and histological mural changes, particularly hypertrophy of the muscle cells and an increase in the intercellular collagen (Pompino and Oerthel-Haid, 1973; Mayo and Hinman, 1976).

The increase in collagen, as shown by electron microscopy (Mayo *et al.*, 1973), occurs in the intercellular spaces between the muscle fibres. However, no observations have been made on the elastic component of the vesical wall and its role has remained uncertain.

From previous studies on dilated ureters in children and in adults, it has been shown that the elastic tissue is involved in the pathological process (Emery and Gill, 1974; Pagano *et al.*, 1976); in particular, there is an increase of elastin, probably to compensate for the raised internal pressure. Relief of the obstruction restores normal morphology (Pagano *et al.*, 1976).

In the obstructed urinary bladder the increased thickness of the wall is mainly due to muscle hypertrophy; the connective tissue does not increase in the same proportion. In chronic obstruction there is decreased muscle contractility and dilatation of the intercellular spaces with collagen formation, as shown by electron microscopy (Mayo and Hinman, 1976).

In children, obstruction of the bladder is accompanied by an increase in the thickness of the wall, largely the result of muscle hypertrophy. No extensive studies have been carried out to determine the roles of collagen and elastin.

The purpose of this work was to carry out chemical and histological studies on the connective tissue fibres, collagen and elastin, in the normal and in the obstructed bladder in children. The effects of chronic obstruction were also studied in the adult bladder.

Materials and Methods

Normal bladders were removed at autopsy from children aged between 3 months and 8 years. The abnormal material consisted of biopsies taken during operations on children with urethral valves. Material from normal and pathological adult bladders was taken at autopsy of individuals aged between 48 and 70 years.

One centimetre of each specimen was used for the histological study, using the Van Gieson, haematoxylin and eosin and Weigert's resorcin-fuchsin stains.

Chemical purification of the elastic tissue was achieved with the autoclave and O.1N NaOH methods as previously described (Pagano *et al.*, 1976; Abatangelo *et al.*, 1977).

The amount of collagen was calculated from the hydroxyproline content by assuming that OH-proline is 14% in weight of the total collagen.

The amino acid analyses were performed after

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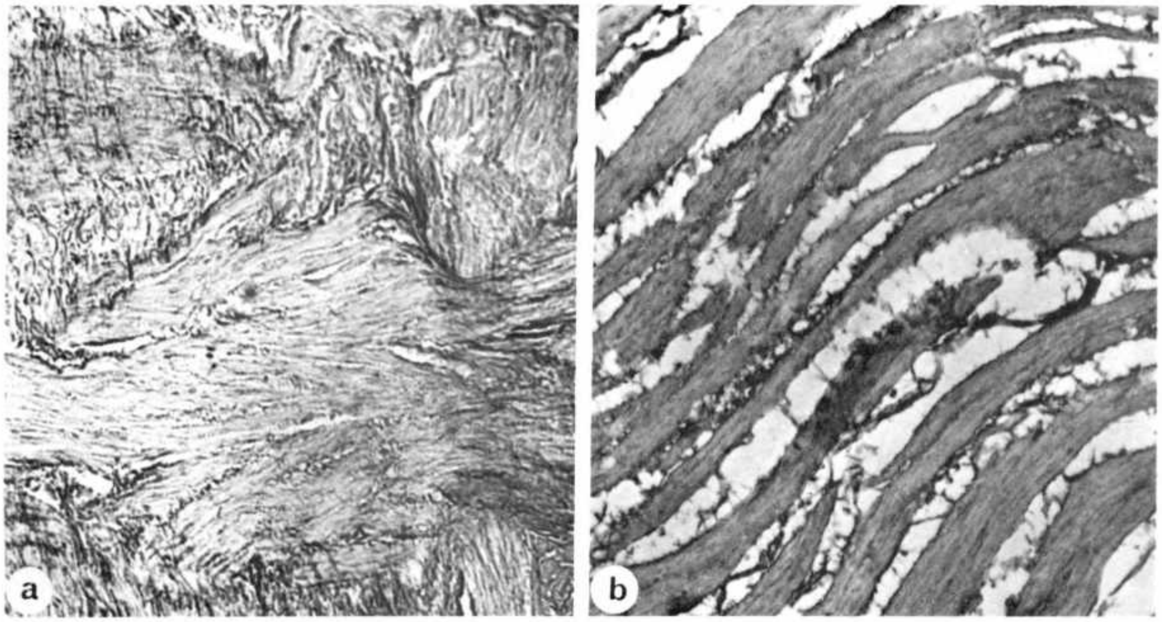

Fig. 1 (a) Surgical specimen of pathological urinary bladder of 3-month-old child. The elastic fibres are abundant and are surrounding the muscle cells. (b) Surgical specimen of normal urinary bladder of 3-month-old child. Scanty elastic fibres in the muscle layer (Elastin stain × 100).

acid hydrolysis in 6N HCl at 110°C for 22 h using an amino acid analyser JLC 5AH.

Results

The histological structure of the normal and the obstructed bladder in children aged 3 months is shown in Figure 1.

It is evident that, apart from the muscle hypertrophy in obstructed cases, there is an increase in elastic tissue and the fibres are closely associated with the muscle elements. Quantitative estimation of the connective tissue was not possible because of the very limited quantity of pathological material taken during the surgical operations.

The histological appearances of the normal and the obstructed bladder in children aged between 4 and 8 years showed no significant differences in connective tissue content. Quantitatively, the elastin and collagen, calculated as a percentage of the total weight of the bladder, were also similar (Table 1).

Table 1 Collagen and Elastin Content

	Dry weight (g%)	
	Collagen	*Elastin*
Normal urinary bladder 4 years	29.3	1.17
Abnormal urinary bladder 8 years	30.9	1.17
Normal urinary bladder 63 years	28.6	2.42
Abnormal urinary bladder 68 years	28.8	3.80

In the adult there was a significant histological difference between the normal and the chronically obstructed bladder (Fig. 2). The elastin fibres were more abundant in the pathological organ, while in the normal bladder they were scanty in number and more fragmented.

The quantitative estimation is shown in Table 1, which illustrates the increase in elastin (30-35%). The collagen, calculated from the hydroxyproline content, does not differ significantly.

Discussion

It is evident that the wall of the obstructed bladder in 3-month-old children is very rich in elastic fibres as compared with the normal. The fibres are distributed in all of the layers and between the muscle elements. No quantitative estimation of the elastin and collagen content was made because the specimens taken during the surgical operations were too small. There were no significant histological differences between the normal and the obstructed bladder in children aged between 4 and 8 years.

The discrepancy in the histological findings between the newborn and the 4 to 8-year-old children

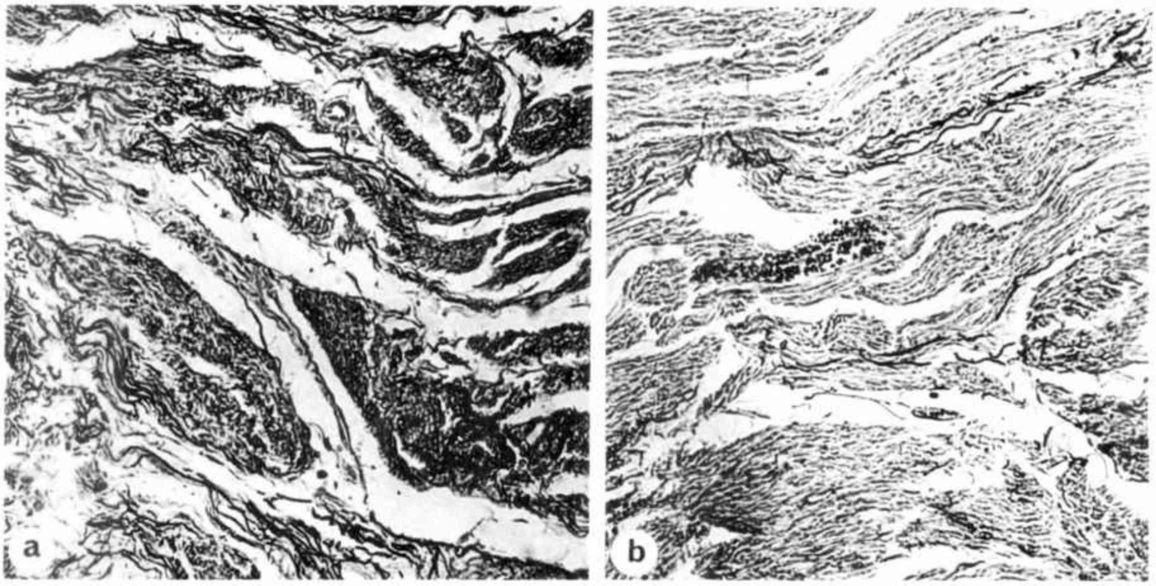

Fig. 2 (a) Adult pathological bladder in which the elastic fibres are abundant and well represented in the muscle layers. (b) Normal adult bladder. The elastic fibres are sparsely represented in the muscle layers (Elastin stain × 100).

is probably due to the nature of the obstruction, which was more severe in the former than in the latter. Unlike the infant cases, it was possible to measure the elastin content chemically. There was no difference quantitatively between the obstructed and the unobstructed cases (Table 1).

From the amino acid analyses it was seen that the elastin of the pathological organ was richer in polar amino acids (aspartic acid, threonine, serine, glutamic acid, lysine, histidine and arginine) than the normal bladder (Table 2). This indicates that the glycoprotein moiety (Gotte and Serafini-Fracassini, 1963; Gotte *et al.*, 1963) is more firmly attached to the elastin than in the normal and, consequently, is not easily removed by the alkali treatment (see Methods).

Table 2 Amino Acid Composition of Purified Elastin Obtained from Normal and Abnormal Urinary Bladders (Amino Acid Residues per 1000 Residues)

Amino acid	*Normal urinary bladder (4-8 years)*	*Abnormal urinary bladder (4-8 years)*	*Normal urinary bladder (adult)*	*Abnormal urinary bladder (adult)*
OH-Proline	13.2	16.2	17.4	19.7
Aspartic acid	4.1	7.0	10.5	14.0
Threonine	9.0	8.8	13.4	12.0
Serine	8.3	8.9	11.2	12.6
Glutamic acid	18.4	23.7	28.5	31.0
Proline	120.9	119.7	118.2	104.6
Glycine	314.7	310.8	290.9	295.9
Alanine	238.9	231.5	224.2	230.6
Valine	136.5	132.5	127.3	134.0
Methionine	Trace	Trace	1.1	1.2
Isoleucine	24.8	25.4	24.8	23.4
Leucine	61.4	61.7	60.7	48.9
Tyrosine	2.7	3.8	15.2	7.1
Phenylalanine	24.6	25.1	25.6	30.9
Isodesmosine	1.9	1.5	2.4	1.8
Desmosine	2.7	4.0	2.4	2.2
Lysine	7.6	6.8	9.0	12.5
Histidine	1.4	2.2	3.2	3.1
Arginine	8.1	9.9	13.0	13.9

In the urinary bladder of the adults (48-70 years) the histological picture showed a difference between the normal and hypertrophic organs. As shown in Figure 2, the elastic fibres were more abundant in the obstructed bladder.

The elastic fibres were distributed in all layers; this was best seen in the histology of the bladder of the 3-month-old children.

From a quantitative point of view the elastin extracted from the chronically obstructed bladders in adults was significantly increased when compared with the normal (Table 1). The amino acid composition showed the same differences as in the 4 to 8-year-old age group. In fact, the polar amino acids in the adult pathological cases showed an increase.

No significant variation in collagen content was observed in any of the age groups (Table 1).

It is concluded that, in addition to the muscle, the connective tissue of the obstructed bladder undergoes modifications.

Especially in the newborn and in the chronically obstructed adult bladders, histological studies showed muscle hypertrophy and an increase in elastic fibres such as can be seen in dilated ureters in chidlren (Pagano *et al.*, 1976).

Unexpectedly, the obstructed bladder of the 4 to 8-year-old children did not show the same differences in elastin content. However, in all cases a common aspect of the molecular pathology of the elastin was the alteration in amino acid composition which, in the elastin of the pathological organs, showed increased polar amino acids. As already described in dilated ureters (Pagano *et al.*, 1976) and in atherosclerotic aortas (Gotte *et al.*, 1965), this increase has to be correlated with pathological conditions such as increased hydrostatic pressure, atherosclerosis, etc.

The ageing process seems to produce similar effects on the chemical composition of elastin which in the normal urinary bladder shows a progressive increase in polar residues with increasing age.

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Comparison of Cephazolin and Gentamicin in the Prophylactic Treatment of Infection in Out-patient Urinary Tract Endoscopy

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Summary—Previous studies have shown that the incidence of rigors following urinary tract endoscopy in out-patients may be as high as 16% and that this incidence can be significantly lowered to about 7% by the administration of intramuscular cephazolin sodium at the time of endoscopy. In order to reduce further the rigor rate, a comparison of intramuscular cephazolin with gentamicin has been carried out with 200 patients in each group. There was a rigor rate of 10% and 9% respectively with no significant difference between the 2 drugs. There was no correlation between an infected urine and the occurrence of a rigor. Cephazolin sodium remains the drug of choice in this situation because of its low toxicity.

Barrington and Wright (1930) showed that, following urological endoscopy, a transient bacteriaemia could occur, and since then it has been routine practice in many centres to offer antibacterial chemoprophylaxis to patients undergoing surgical procedures. In other centres, however, antibiotic prophylaxis has been reserved for those patients who had either proven urinary tract infection or some other medical indication for antibiotic treatment. Using a system of pre-paid reply postcards, an incidence of some 10 to 16% of rigors has been reported by patients undergoing these procedures (Hart *et al.*, 1978). It was assumed that this high incidence of rigor was associated with bacteriaemia and subsequent studies showed that while a single dose of intravenous cephazolin given during the operative procedure was ineffective in reducing the incidence of rigor, a similar dose given intramuscularly significantly reduced the rigor rate (Hart *et al.*, 1980).

While recognising that cephazolin was an effective drug when given intramuscularly in this situation, there was still a significant incidence of rigor following endoscopy and the aim of this study was therefore to compare the effect of intramuscular cephazolin with a single dose of intramuscular gentamicin to see which was the more effective.

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Materials and Methods

Four hundred patients were admitted to the study. They were consecutive out-patient admissions to the day-bed unit for urological endoscopy under general anaesthesia and we excluded only those patients who declared an allergy to an antibiotic or who were already taking one for proven existing infection. The patients were randomly assigned to receive either 1 g cephazolin sodium intramuscularly or 80 mg gentamicin intramuscularly at the time of the endoscopy or immediately afterwards. There were 200 patients in each group and the trial was designed as a double blind study. A specimen of urine was taken at the time of instrumentation from all patients and a second specimen prior to their discharge from the day-bed unit some 2 to 4 h after instrumentation. All specimens were cultured from a mid-stream specimen of urine using the dip-slide (Oxoid) technique (Duerden and Moyes, 1976).

Table

	Cards issued	*Cards returned*
Cephazolin	200	187
Gentamicin	200	191
Total	400	378 (94.5%)

Results

Of the 400 postcards issued to the patients 378 (94.5%) were returned (Table). Six patients called out their medical practitioner and 39 (9.75%) reported the occurrence of a rigor in the 24 h following endoscopy. Of these 39 patients 20 (10%) received cephazolin and 19 (9.5%) received gentamicin. Prior to endoscopy 27 patients had an infected urine but none of them had an infected urine culture following endoscopy. Three other patients who had previously sterile urine had a post-endoscopy urine culture which grew in each case *Esch. coli.* All organisms except *Pr. mirabilis* were sensitive to cephazolin but all 5 cultures of *Str. faecalis* were resistant to gentamicin. There seemed to be no correlation between the occurrence of a rigor and the possession of an infected urine either before or after endoscopy, since the 39 patients who had a rigor produced only 3 specimens of urine with a positive culture. Only one patient had a mixed infection comprising *Esch. coli* and *Str. faecalis.*

Discussion

For many years before the antibiotic era "catheter fever" was recognised and was demonstrated by Barrington and Wright (1930) to be due to bacteriaemia following instrumentation of the urinary tract. Because of this it has been a widespread custom to give prophylactic antibiotics to those patients at particular risk, *i.e.* those with cardiac valvular disease or those with recognised infected urine. Opinion has varied, however, regarding the necessity or value of extending this cover to all patients undergoing endoscopy. It has been shown (Hart *et al.*, 1980) that there is an incidence of rigor (up to 16%) following this procedure irrespective of the primary pathological condition and that it can be significantly reduced by the use of intramuscular cephazolin which was chosen as an antibiotic relatively free from side effects, which was excreted in active form in urine and which achieved satisfactory tissue levels (Kozatani *et al.*, 1972). It is also effective against many organisms causing urinary tract infections (Ishigami *et al.*, 1970; Cox, 1973; Gold *et al.*, 1973; Madhavan *et al.*, 1973; Nicholas *et al.*, 1973; Naumann and Reintjens, 1974). However, there still remained a group of patients who in spite of the administration of intramuscular cephazolin experienced a rigor, and for this reason we instituted a search for an even more effective antibiotic. Our initial choice for comparison with cephazolin was gentamicin. This aminoglycoside is currently used in our practice for the treatment of gram-negative septicaemia but its use must be carefully monitored because of side effects, particularly its cumulative effect in patients with renal impairment which may lead to ototoxicity (Wersall *et al.*, 1969). However, it was felt that a single dose intramuscularly would not carry any great risk of ototoxicity.

There was a 10% incidence of rigor among the group receiving cephazolin sodium compared with 9.5% among the group receiving gentamicin. This difference is not, of course, statistically significant. It is of interest that of the 27 patients who had positive pre-operative urine cultures and 3 patients who had positive post-operative urine cultures, only 3 would admit to having had rigor in the 24 h following endoscopy. These results confirm the previous studies in that some benefit may be derived from the prolongation of inhibitory serum levels of antibiotics resulting from their intramuscular use rather than the relatively short duration given by a comparable intravenous dose. It is not clear, however, why some 7 to 10% of patients still have a post-endoscopy rigor, and it may be that the release of endotoxins is a key factor rather than the actual cultured presence of organisms in the urine.

In the context of this study on out-patients it was not possible to carry out serial blood cultures; as stated above, there is no correlation between the occurrence of rigor and the presence of bacterially infected urine (and therefore probably of bacteriaemia). Blood cultures would not identify those whose rigors are due to endotoxins and further work is needed to try to identify the presence of these substances in the blood stream.

Perhaps a different antibiotic and possibly an alternative route of administration should be used. Cephazolin is ineffective in these circumstances when given intravenously (Hart *et al.*, 1978) and it may be that an antibiotic given orally before and immediately after endoscopy would be more effective.

However, given that there is no difference between cephazolin and gentamicin in reducing the incidence of rigor in these patients, we shall continue to use cephazolin because, theoretically at least, it is less toxic. However, further studies are being carried out to find an antibiotic and route of administration which will further significantly reduce the incidence of these complications.

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Primary Neoplasm in Vesical Diverticula

A Report of 12 Cases

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Summary—Twelve patients with primary carcinoma arising in a vesical diverticulum are presented. Treatment included diverticulectomy with or without post-operative irradiation and transurethral resection. Recurrences were detected in 6 patients and the disease-free survival rate was 8%.

Carcinoma arising in a vesical diverticulum is rare. The incidence varies from 2 to 7% (Boylan *et al.*, 1951; Knappenburger *et al.*, 1960; Fox *et al.*, 1962; Kelalis and McLean, 1967; McLean and Kelalis, 1968). The accepted treatment is diverticulectomy; however, the survival of such patients has been uniformly poor. In this report, 12 patients with primary neoplasm arising in a vesical diverticulum are presented and the clinical course of the disease is discussed.

Materials and Methods

The records of 850 patients with carcinoma of the bladder seen at Stanford between 1962 and 1977 were reviewed. Twelve patients had a primary neoplasm arising in a bladder diverticulum. Excluded were those patients with concomitant tumours elsewhere in the bladder.

Results

There were 10 males and 2 females. The ages ranged between 47 and 83 years (Table 1). Eight patients presented with gross haematuria; and in the remaining 4 the tumours were discovered on cystoscopy performed for obstructive symptoms in 3 and for recurrent cystitis in one. Excretion urography was diagnostic of a bladder tumour in only 2 patients. Although in 4 patients a diverticulum was seen on the cystogram phase of the excretion urogram, a filling defect could not be identified within these diverticula.

Table 1 Age of Patients

Age (years)	*No. of patients*
40-49	1
50-59	5
60-69	0
70-79	4
80-89	2
Total	12

There were 10 transitional and 2 squamous cell carcinomas (Table 2). One patient with squamous cell carcinoma had a stone within the diverticulum in which the tumour arose. Of the 10 transitional cell tumours, 9 were papillary and one was carcinoma *in situ*. Of the 9 papillary tumours, 2 were grade II, 4 were grade III and 3 were grade IV. Invasion of the wall of the diverticulum and/or the perivesical tissues was found in 8 of 12 patients. None of the patients had evidence of metastatic disease at the time of definitive therapy.

Treatment was diverticulectomy in 8, diverticulectomy followed by irradiation with 7000 rads in 2, and transurethral resection in 2 patients (Table 3).

Recurrent bladder tumours developed in 5 patients within one year and in 1 patient in 3

Table 2 Pathology

	No. of patients
Transitional cell carcinoma (10 patients)	
Carcinoma *in situ*	1
Grade II	2
Grade III	4
Grave IV	3
Squamous cell carcinoma (2 patients)	
Grade II	2
Total	12

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Table 3 Treatment

	No. of patients
Diverticulectomy	8
Diverticulectomy and irradiation	2
Transurethral resection	2
Total	12

years. In 4 of the 6 patients the recurrent tumours were of a higher grade and/or stage than the original tumour (Table 4). Five of the remaining 6 patients died of metastatic disease before local bladder recurrences could be detected.

Nine patients died of their disease within 4½ years. Two patients are alive with disease at 2 and 3 years, and 1 patient is free of disease at 3½ years (Table 5). The disease-free survival rate is 8%.

Discussion

Carcinoma arising in a bladder diverticulum presents a problem in management. The literature (Boylan *et al.*, 1951; Knappenburger *et al.*, 1960; Siegel, 1974; Redman *et al.*, 1976) reveals a uniformly poor survival rate except for the report by Montague and Boltuch (1976) in which only 2 of 10 patients died as a result of their disease. In the present series, which is comparable to that of Montague and Boltuch with regard to the incidence of invasion and the mode of therapy, only 3 of 12 patients are alive at 2, 3, and 3½ years—2 with and 1 without disease. Our experience with such a poor survival is similar to that of Kelalis and McLean (1967) and others (Siegel 1974; Redman *et al.*, 1976).

The main factor affecting survival seems to be the presence or absence of invasion. Seven of 8 patients with invasion died of their disease compared to only 2 of 4 patients without invasion. It has been pointed out by Kelalis and McLean (1967) that the high grade nature of these tumours, together with the thinness of the diverticular wall, is responsible for early peridiverticular invasion, a condition which precludes successful operative management and adds to the poor survival rate.

Recurrences after diverticulectomy occurred in 4 of 10 patients. Five of the remaining 6 patients succumbed to their disease before recurrences could be detected. This high recurrence rate is the same as that for non-diverticular bladder

Table 4 Recurrences

	Primary tumour			*Recurrent tumour*					
Patient	*Grade*	*Invasion*	*Treatment*	*Interval (months)*	*Grade*	*Stage*	*Treatment*	*Outcome*	*Residual tumour*
A M.	II	No	TUR	3	IV	B 2	Radiation	Dead	Yes
E.L.	IV	Yes	TUR	6	IV	B 2	Cystectomy	Dead	Yes
H H.	III	Yes	Diverticulectomy	7	III	B 2	Radiation	Dead	Yes
I.I	II	Yes	Diverticulectomy	11	III	B 2	Radiation	Dead	Yes
A.H	IV	Yes	Diverticulectomy	12	IV	B 2	TUR	Alive	Yes
A.B.	CIS	No	Diverticulectomy	36	III	C	Cystectomy	Alive	Yes

Table 5 Survival

Patient	*Cell type*	*Grade*	*Invasion*	*Alive (months)*	*Dead (months)*	*Residual tumour*
A.M.	Transitional	II	No		40	Yes
I.I	Transitional	II	Yes		40	Yes
J.C.	Transitional	III	No	40		No
H.H	Transitional	III	Yes		36	Yes
P.A.	Transitional	III	Yes		10	Yes
P.P.	Transitional	III	Yes		18	Yes
A B	Transitional	CIS	No	36		Yes
A H.	Transitional	IV	Yes	24		Yes
A.M.	Transitional	IV	Yes		18	Yes
E.L.	Transitional	IV	Yes		12	Yes
H.B.	Squamous	II	Yes		2	Yes
J.K.	Squamous	II	No		54	Yes

neoplasm, suggesting that the aetiological factors in both diseases are the same. This may be contrary to the belief that stasis and chronic inflammation are responsible for the development of carcinoma in the wall of the diverticulum (Kelalis and McLean, 1967).

It is concluded that although diverticulectomy is the standard treatment for primary diverticular tumours, because of the poor survival rate after diverticulectomy and the high incidence of recurrent tumours, a more aggressive therapy directed towards the whole bladder should be seriously considered. We suggest that an invasive primary diverticular neoplasm should be treated in the same manner as a non-diverticular bladder tumour, namely with pre-operative irradiation followed by radical cystectomy with or without post-operative chemotherapy, depending on the status of the regional lymph nodes.

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The Safety of Transrectal Biopsy of the Prostate as an Out-patient Investigation

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Summary—The complications following transrectal prostatic biopsy are reviewed in 150 patients.

The most frequent complications were urinary infection and pyrexia.

A prospective study within the reported series demonstrated a high incidence of bacteriaemia following biopsy.

The results suggest that transrectal prostatic biopsy may be performed safely as an out-patient procedure without the use of prophylactic antibiotics, although antibiotic therapy may be indicated when complications do arise.

In 1937 Astraldi described a technique for transrectal biopsy of the prostate which over the years has been modified and is now used widely because of its simplicity and relatively high degree of accuracy (Bissada *et al.*, 1977). This paper reviews 150 prostatic biopsies carried out in 129 patients and seeks to demonstrate the relative safety of the procedure on an out-patient basis.

Patients and Methods

One hundred and twenty-nine patients (age range 47 to 88 years) were included in the series. The case histories were reviewed retrospectively but the total number includes a prospective study involving 20 patients.

The majority of patients were attending the clinic for the first time but 30 were involved in a multicentre trial of therapy for carcinoma of the prostate and were returning for repeat biopsies as part of that study.

All biopsies were performed by either a Consultant or Registrar in the out-patient clinic with the patient in the left lateral position, knees to chest, and employing a Tru-Cut biopsy needle (Travenol Laboratories, Illinois, USA). Each patient had 2 or 3 biopsies taken at the same time, using the same needle.

No patient received any form of bowel washout or antibiotic cover. Patients already on antibiotic therapy or those in whom it was indicated for pre-existing disease, *e.g.* rheumatic heart disease, were excluded. No other instrumentation of the urinary tract was performed in any of the patients in the series.

In the prospective part of the series 20 patients undergoing transrectal prostatic biopsy had blood cultures taken at 10 and 30 min after the biopsy. Urine cultures were performed at 1 h and 24 h after the biopsy. The same procedure was carried out with a control series of 10 patients having rectal examinations but not having biopsies. The results of this series are shown in Table 2.

All patients were warned of the possible complications of pyrexia and urinary symptoms following the procedure and were instructed to return directly to hospital should any such problem arise.

Results (Tables 1 and 2)

Twenty-one patients (14%) returned to hospital within 24 h complaining of feeling hot and sweaty.

Table 1 Frequency of Complications in 150 Transrectal Prostatic Biopsies

Complication	*No. of biopsies*	*Total biopsies (%)*	*No. of patients admitted*
Urinary infection	30	20.0	0
Pyrexia	21	14.0	4
Haematuria	7	4.6	1
Retention of urine	4	2.6	4
Rectal bleeding	1		
Prostatic abscess	1	2.0	1
Epididymo-orchitis	1		

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Table 2 Results of Prospective Study of Patients Having Transrectal Biopsy

Investigation	*No. of patients (Total = 20)*	*Controls: no biopsy (Total = 10)*
Positive blood culture at 10 min	17 (85%)	0
Positive blood culture at 30 min	0	0
Positive urine culture at 1 h	1 (5%)	0
Positive urine culture at 24 h	1 (5%)	0
Pyrexia within 24 h	3 (15%)	0

All had a temperature in excess of 37.5°C and 4 had had rigors. Blood and urine cultures were carried out in all cases and in only 2 were blood cultures positive, coliform organisms being grown in each case.

Urine cultures demonstrated infection in only 9 cases. Of this group only 4 required hospital admission. All had had rigors and all had a pyrexia in excess of 38°C. The remainder were treated with oral ampicillin and were reviewed at 48 h, when they were apyrexial and asymptomatic. Of the 4 patients requiring hospital admission one developed septicaemia, *Esch. coli* being grown on blood culture on 2 separate occasions. This patient was treated with gentamicin and ampicillin and made a rapid recovery but remained in hospital for 8 days. The remaining 3 patients were treated with ampicillin and were discharged within 48 h.

Urinary tract infection proven on culture of a mid-stream specimen of urine developed in 30 patients (20% of the total) including 9 patients with pyrexia after biopsy. The remaining 14 patients with sterile urine at the time of biopsy developed symptomatic urinary tract infection over the following 7 days. A further 7 patients had asymptomatic urinary infections proven on culture at subsequent clinic attendance. The infecting organisms were *Esch. coli* (80%) and *Proteus* species (20%).

Acute retention of urine was precipitated by the biopsy in 4 patients, including one patient with clot retention from profuse haematuria.

Seven patients complained of frank haematuria; 5 of these were transient and cleared without requiring admission. One patient developed clot retention (see above) and one patient (who was subsequently found to have carcinoma of the prostate) developed severe haematuria persisting for over 24 h, during which time his haemoglobin fell from 13.3 to 8.6 gs/dl, necessitating transfusion.

One patient with a pre-existing asymptomatic urinary infection developed acute epididymo-orchitis 3 days after biopsy.

One patient returned to hospital complaining of rectal bleeding persisting for more than 6 h after biopsy but did not require admission.

A further patient developed a prostatic abscess which discharged spontaneously, leaving a urinary fistula into the rectum.

In the prospective study (Table 2), 17 out of 20 patients (85%) having transrectal biopsies of the prostate had positive blood cultures at 10 min after biopsy (12 cases *Esch. coli*, 4 *Str. faecalis* and one case *Proteus*). No patient had a positive blood culture at 30 min after biopsy. Similarly, only one patient had bacteriuria and subsequent urinary infection and this may have been pre-existing. Only 3 patients (15%) developed pyrexia.

Discussion

In previously reported series of transrectal prostatic biopsy, urinary tract infection has had an incidence varying from 38.5% (Fawcett *et al.*, 1975) to 17% (Dowlen *et al.*, 1974) and pyrexia after biopsy has had an incidence of 38% (Bissada *et al.*, 1977) to 27.4% (Davison and Malament, 1971). Fawcett *et al.* (1975) reported an unacceptably high incidence of urinary infection (38.5%) in a retrospective study and recommended that antibiotic cover be provided for transrectal prostatic biopsy. Bissada *et al.* (1977) in a prospective series demonstrated that pyrexia following biopsy could be significantly reduced (from 38 to 21%) by the administration of an antibiotic before the biopsy procedure, but that antibiotic therapy started at the time of biopsy had no such beneficial effect. Similarly, the use of antibiotics did not produce a significant decrease in the incidence of urinary infection.

In this series the incidence of urinary infection was 20% and the incidence of pyrexia was 14% following transrectal biopsy. The prospective part of the study demonstrated that 85% of patients developed transient bacteriaemia as a result of the biopsy but only 15% developed pyrexia.

On the basis of these results it is clear that antibiotic cover should be provided for "high risk" patients, *e.g.* those with rheumatic heart disease, but otherwise it is probably best reserved for patients developing urinary infection or pyrexia where there is a definite indication.

Whilst there is undoubtedly a certain morbidity associated with transrectal prostatic biopsy, in this series only 10 patients (6% of all biopsies) required hospital admission. Thus, despite the recommendation of Dowlen *et al.* (1974) that all patients be admitted for prostatic biopsy, this series supports the view that it may be performed safely in the Out-patient Clinic as and when indicated by the clinical examination, thereby shortening the time of investigation and also relieving the pressure on in-patient beds and staff. The possible complications must be made known to the patient himself, however, so that immediate consultation and admission can be arranged if indicated.

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Suppressive Effects of Surgical Stress on Circulating Androgens During and After Prostatectomy

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Summary—Changes in circulating testosterone (T) and dihydrotestosterone (DHT) levels were investigated 2 days before and 2, 7, 30 and 60 days after retropubic prostatectomy in 28 patients with benign prostatic hypertrophy. Following operation the concentrations of both steroids declined and reached minimal levels 2 days after surgery. One month post-operatively testosterone had recovered to its pre-operative value, whilst the recovery of dihydrotestosterone to its pre-operative level required a minimum period of 2 months. These data indicate the need for careful interpretation of any androgen measurement following surgery.

The view that major surgical stress would influence the levels of circulating steroids and peptide hormones has gained much experimental support. A significant increase in serum prolactin and growth hormone was observed by Noel *et al.* (1972) during surgery. Significant changes in the concentration of plasma testosterone and luteinising hormone have also been reported during and after surgery in patients undergoing either pulmonary lobectomy or gastrectomy (Aono *et al.*, 1972). The most profound change has been found to be that of plasma testosterone, which significantly declined after the operation. Previous studies by Matsumoto *et al.* (1970) and Aono *et al.* (1972) on patients undergoing various operations have also demonstrated a post-operative decrease in the level of plasma testosterone in all of the male patients. These investigators found that the concentration of testosterone following minor or moderate operations would return towards its pre-operative level after one week, whereas in the case of major operations the decreased level of testosterone was maintained for 2 to 3 weeks following surgery.

In patients with benign prostatic hypertrophy, surgery is still the most acceptable mode of treatment. The non-surgical treatment of this disease has gained little progress and requires more precise and controlled trials (Chisholm, 1970; Scott and Coffey, 1975). However, some factors influencing the endocrine control of this disease have been investigated. Dihydrotestosterone has been implicated in the aetiology of BPH and elevated levels of this steroid have been reported in both BPH tissues (Siiteri and Wilson, 1970) and circulating blood (Ghanadian *et al.*, 1977) of patients. Limited information is available on the concentration of testosterone and dihydrotestosterone in blood following prostatectomy. In a preliminary study, Mahoudeau *et al.* (1974) reported that there was no difference in either serum testosterone or dihydrotestosterone following prostatectomy. However, their sampling collection varied between 9 and 34 days after operation. Vermeulen and De Sy (1976) have measured and compared the levels of these 2 steroids 1 to 3 days pre-operatively and 2 to 5 months post-operatively, but did not follow the changes of these hormones during the period of the operation or for the first 2 months afterwards. Therefore this study was designed to investigate the changes of circulating testosterone and dihydrotestosterone before and up to 2 months after the operation, in patients with benign prostatic hypertrophy undergoing retropubic prostatectomy.

Materials and Methods

Twenty-eight patients with benign prostatic hypertrophy aged between 67 and 80 years, undergoing retropubic prostatectomy were studied. Benign prostatic hypertrophy was established in all patients by histological examination of the operative specimen. Blood samples were drawn 2 days before

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Table Serum Androgen Levels in Patients with Benign Prostatic Hypertrophy Before and After Retropubic Prostatectomy

Time of sampling	*No. of samples*	*Testosterone*		*Dihydrotestosterone*	
		Mean ± SEM n mol/l	*Significance (value for P)*	*Mean ± SEM n mol/l*	*Significance (value for P)*
2 days pre-operative	28	16.73 ± 1.04		2.41 ± 0.20	
2 days post-operative	28	4.95 ± 0.54	<0.001	0.85 ± 0.06	<0.001
7 days post-operative	27	8.19 ± 1.11	<0.001	1.28 ± 0.20	<0.001
1 month post-operative	10	13.97 ± 1.59	N.S.	1.62 ± 0.23	<0.01
2 months post-operative	6	17.00 ± 1.33	N.S.	2.33 ± 0.52	N.S.

Post-operative values for testosterone and dihydrotestosterone have been compared with pre-operative values and their significance (values for *P* expressed). (N.S. = not significant.)

and 2, 7, 30 and 60 days after operation. All blood samples were drawn between 10.00 and 12.00 h. Plasma was separated within half an hour and the samples were stored at –20°C prior to assay.

Testosterone and dihydrotestosterone were measured by a sensitive radioimmunoassay following separation of testosterone from dihydrotestosterone by thin layer chromatography (Ghanadian *et al.*, 1975). The sensitivity and reliability criteria of the method for human serum have been reported previously (Lewis *et al.*, 1976).

Results

Testosterone and dihydrotestosterone were measured 2 days prior to operation and were considered to be basal values. These results were compared to values obtained 2, 7, 30 and 60 days after the operation (Table). As can be seen from the results, there were significant decreases in the levels of both T and DHT 2 days and 7 days after the operation. One month later there was no statistical difference between the level of testosterone and its pre-operative value ($P > 0.1$), whilst at 2 months the testosterone value had returned to its pre-operative levels. However, DHT displayed a delayed recovery. It was lower than the pre-operative level even after 30 days ($P < 0.01$), eventually recovering after 2 months.

Discussion

This study demonstrates that the surgical effects of prostatectomy profoundly suppress the circulating androgen levels. The recovery of androgens appears to be slow and it takes at least one month for testosterone and 2 months for dihydrotestosterone to reach their pre-operative basal levels. The decline in plasma testosterone following prostatectomy is in accordance with the suppressive effects of other types of surgery on testosterone secretion reported by Aono *et al.* (1972). However, these workers followed up testosterone changes for the first 6 days only. The present data reveal that both testosterone and dihydrotestosterone decline within the first 48 h following operation, reaching their minimal levels after 2 days, and then gradually increasing. The full recovery of dihydrotestosterone to its pre-operative level requires a period of 2 months. This delay in the recovery of DHT could be explained by the fact that a great proportion of the circulating DHT is derived from the peripheral conversion of testosterone (Ito and Horton, 1971). Furthermore, it has been reported that about 50% of the peripheral DHT in elderly men with BPH comes from sources other than the testes (Ishimaru *et al.*, 1977). These findings suggest that the full restoration of peripheral testosterone is necessary before further peripheral conversion can take place and restore the DHT to its basal values.

The present study shows that surgical stress profoundly affects the secretion of testosterone by the Leydig cells since most of the blood testosterone originates from the testes. The short-term effects of surgical stress on the relationship between the testosterone and luteinising hormone levels have been investigated (Charters *et al.*, 1969; Aono *et al.*, 1972; Carstensen *et al.*, 1973). However, there is a paucity of information with regard to the long-term effects of surgery on the pituitary-gonad axis. Aono *et al.* (1972) showed that plasma LH increased significantly from the pre-operative level during the operation and reached its maximum concentration 30 min after the primary incision had been made. Thereafter it decreased and exhibited a significant fall 2 days after surgery. These workers suggested a lack of testicular sensitivity to gonadotrophins during and following major surgery, though a shift in the androgen biosynthetic pathway of the testis may be considered. Wang *et al.* (1976) have reached a similar conclusion following their experiments, when they injected 50 μg of luteinising hormone releasing hormone (LHRH) to patients on the first pre-operative and post-operative days. Post-operatively the LH response was increased compared with its pre-operative value. However, the expected testosterone response during the post-operative day was not observed. They postulated that this could be due to a decrease in sensitivity of testosterone secretion to LH following surgical stress.

It can be concluded from this study and that of others (Aono *et al.*, 1972; Carstensen *et al.*, 1973; Wang *et al.*, 1976) that the decline in circulating testosterone is the most prominent feature following surgery in male patients. The slow recovery of both testosterone and dihydrotestosterone indicates the necessity for careful interpretation of any androgen measurement following surgery, for the measurement of these 2 androgens is frequently performed when studying the aetiology and biochemistry of both benign hypertrophy and carcinoma of the prostate.

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Leukaemic Infiltration of the Prostate

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Summary—A biopsy of the prostate should be done in lymphoma/leukaemic patients suffering from urinary obstruction. Patients with a lymphomatous infiltration of the prostate should be irradiated and not subjected to surgery.

Two such cases successfully irradiated are described and the present literature is reviewed.

With prolonged survival and longevity of the lymphoma/leukaemic patient there is an increasing number of geriatric problems, amongst which is retention of urine in the male. This is usually due to prostatic hypertrophy and the policy of our department is to operate on such patients. The operative and post-operative courses are usually uneventful and do not differ from those of non-lymphomatous patients. On rare occasions, retention is due to lymphomatous infiltration of the prostate, and irradiation of the prostate appears to be the treatment of choice. We have treated 2 such patients in the last 4 years, with good results.

Case Reports

Case 1. A 73-year-old male was admitted in July 1974 because of urinary retention. A year prior to his admission the diagnosis of chronic lymphatic leukaemia (CLL) had been established elsewhere.

On admission he was catheterised. His prostate was found to be enlarged, homogeneous and elastic in consistency. Peripheral blood count (31,300 leucocytes, 80% lymphocytes) and bone marrow biopsy (infiltration by small homogeneous lymphocytes) confirmed the previous diagnosis of CLL. Excretion urography demonstrated normal kidneys and a filling defect in the base of the bladder due to an enlarged prostate. Histological examination of prostatic tissue obtained by a perineal needle biopsy showed only a few preserved prostatic glands. The normal structure was obliterated by masses of closely packed small lymphocytes (Figs. 1, 2).

The patient received cobalt therapy. An anterior field 12 × 12 cm and a posterior field 18 × 23 cm were irradiated over a period of 11 days. The catheter was removed after 2100 rads. All urological complaints disappeared after the total dose of 2700 rads.

The patient returned in January 1977 with an exacerbation of his leukaemia (70,000 leucocytes) and urinary retention. The prostate was enlarged again. Another dose of 2000 rads of Co was administered to an anterior field 9 × 7 cm and a posterior one 9 × 8 cm over a period of 11 days. After this treatment he could void freely again and was discharged; further treatment of his leukaemia was arranged on an out-patient basis.

Case 2. An 82-year-old male was referred to the Haematology Clinic in 1974 because of CLL found on routine blood count. Physical examination revealed a few enlarged lymph nodes but no hepatosplenomegaly. Haemoglobin was normal; the peripheral blood count showed 15,000 white blood cells with 55 to 65% small lymphocytes. Since the patient was symptom-free, no treatment was administered.

Three months later he complained of abdominal pain. An abdominal aortic aneurysm was diagnosed and operated on successfully.

In May 1978 he was admitted because of urinary retention and fever. Peripheral white blood cells at that

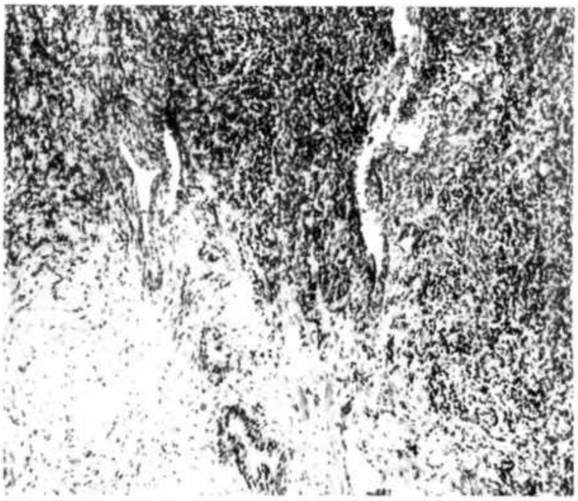

Fig. 1 Needle biopsy specimen shows prostatic glands separated by dense lymphocytic infiltration (H and E × 100).

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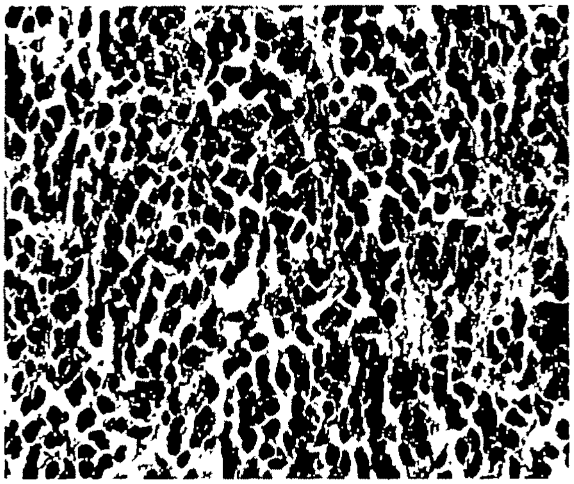

Fig. 2 In higher magnification the infiltration is composed of closely packed lymphocytes (H and E×400).

time were 25,000 with 70% lymphocytes. The prostate was found to be homogeneously enlarged. Excretion urography confirmed the existence of an enlarged prostate. Histological examination of the prostatic tissue obtained by perineal needle biopsy showed a very similar pattern to that of the previous patient, namely an infiltration by small lymphocytes. The patient was treated by antibiotics and the prostatic area was irradiated with a total of 1600 rads. Voiding returned to normal and rectal examination showed a clear shrinkage of the prostatic gland. The patient has been symptom-free since then.

Discussion

Leukaemic infiltration of the genitourinary tract is rare (Lucia *et al.*, 1952). Rader in 1974 counted only 17 cases in the literature. Watson *et al.* (1949) found 13.5% involvement in 234 leukaemic patients; however, involvement was higher (43.3%) in post mortem examinations. Dajani and Burke (1976) reported 56 cases from the literature and added a case of their own.

Jacobi *et al.* (1937) were the first to report lymphatic infiltration of the prostate, diagnosed after a 2-stage prostatectomy in a 78-year-old patient. Fishman and Taylor (1963) were the first to make a pre-operative diagnosis by perineal needle biopsy, and to treat the patient by external irradiation (1100 rads) over a 6-day period. Pre-operative irradiation has already been used, but irradiation was directed to the spleen and spray irradiation to the body, and not to the prostate (Johnson and Gundersen, 1953). Entz and Kruse (1961) reported a transurethral resection of the prostate in a leukaemic patient, followed by irradiation to the suprapubic area (600 rads).

In a previous report (Merimsky *et al.*, 1974), we discussed the problem of prostatectomy in a leukaemic patient. In all of our operations on leukaemic patients since then we have not encountered post-operative coagulation problems or leukaemic exacerbation.

Our present policy, as recognised also by Fishman (1977), is to perform a perineal needle biopsy in all lymphoma/leukaemic patients suffering from urinary obstruction due to an enlarged prostate. Those with a simple prostatic adenoma are operated on. On 2 occasions in the last 4 years where we found leukaemic infiltration of the prostate, the patients were irradiated with excellent results.

We think that even a course of irradiation is preferable to operation on a prostate infiltrated with lymphocytes. The results of such an operation are unpredictable.

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Flutamide in the Treatment of Metastatic Carcinoma of the Prostate

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Summary—Twenty-five patients with metastatic carcinoma of the prostate were treated with Flutamide, a non-steroidal anti-androgen. All patients showed progression; the longest response was 120 weeks. The side effects were nausea, vomiting, breast tenderness and gynaecomastia.

The palliative effect of Flutamide, a non-steroidal anti-androgen, has been reported to be equal to or even superior to that of stilboestrol in advanced carcinoma of the prostate (Neri and Monahan, 1972). Structurally, Flutamide is an anilide (4-nitro-3-trifluoromethylisobutyranilide) that is neither androgenic, oestrogenic, anti-oestrogenic, progestational nor anti-progestational (Spencer Munroe; personal communication). It does not inhibit gonadotrophins and has no adrenocortical activity. Thus this drug, unlike stilboestrol, should not be associated with any side effects. We report our experience with Flutamide in patients with metastatic carcinoma of the prostate.

Patients and Methods

Twenty-five patients with skeletal metastases from carcinoma of the prostate were divided into 2 groups: (1) 12 patients with no previous hormonal treatment and (2) 13 patients with failed hormonal treatment.

All patients had had baseline clinical and laboratory pre-treatment investigations which included chest X-ray, excretion urogram, radiological bone survey and radioisotope bone scan for metastatic lesions, methaemoglobin, haematocrit, RBC, WBC and platelet counts, acid and alkaline phosphatases, SGOT, bilirubin, blood urea nitrogen, creatinine, glucose, uric acid, total protein, albumin, calcium, cholesterol, LDH and urine analysis. The data were recorded on flow sheets. Patients were seen at 6-weekly intervals and baseline evaluation was done every 12 weeks.

In this study we have used only 3 terms to evaluate the response to treatment: (1) complete response—disappearance of all evidence of malignant disease; (2) stable—no deterioration in performance status, no loss of weight, subjectively the patient felt better, and (3) progression—new metastatic lesions and/or subjective deterioration of symptoms.

Group 1

Of the 12 patients in this group 11 were evaluable; one patient was removed from the study because he received the treatment for only one week. All were Caucasian with an age range from 55 to 78 years (average 67 years). Histologically, the prostatic carcinoma was poorly differentiated in 6 patients, moderately differentiated in 3 and well differentiated in 3.

Group 2

Of the 13 patients only 7 were evaluable. For various reasons, including death, severe nausea and vomiting, 6 patients did not receive the drug long enough to evaluate its effect. All were Caucasian with ages ranging from 55 to 82 years (average 65 years). Histologically, the prostatic carcinoma was poorly differentiated in 7 patients, moderately differentiated in 2 and well differentiated in 4.

Results

Group 1

All were stable at 12 weeks, but only 3 patients were stable at 24 weeks and 2 at 48 weeks. One of these was stable for 61 weeks and another for 120 weeks. There were no complete responses in

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this group. The patients who showed progression were removed from the study and treated by other methods.

Group 2

Of the 7 evaluable patients only 2 were stable at 12 weeks. One was stable for 20 weeks and the other for 66 weeks. Six patients either did not receive the drug long enough or died within 3 months.

The most common side effects in both groups of patients were gynaecomastia and breast tenderness. Nausea and vomiting were more common in Group 2 than in Group 1 patients. There was no evidence of either haematological or cardiovascular toxicity.

Discussion

Although the mechanism by which Flutamide exerts its anti-androgenic effect is not known, it has been suggested that it may interfere with the uptake of testosterone or dihydrotestosterone by prostatic tissue. Jacobo *et al.* (1976) suggested that it may inhibit the binding of dihydrotestosterone by the nuclear receptor proteins of androgen dependent cells such as the prostatic acini.

In the seminal vesicles and ventral prostate of male rats the compound antagonises the effects of testosterone and dihydrotestosterone to the same extent as cyproterone acetate. The compound also produces hypospadias and abnormal development of the vaginal tract and scrotum (Spencer Munroe; personal communication). In humans the drug is rapidly metabolised shortly after administration and at high doses produces elevation of serum luteinising hormone and does not decrease the levels of plasma testosterone (Prout *et al.*, 1975). In fact, plasma testosterone may rise to high normal levels with Flutamide treatment.

It is evident from this limited, uncontrolled study that Flutamide has an effect on untreated patients with advanced carcinoma of the prostate and this was also the experience of Prout *et al.* (1975). However, only 2 patients in Group 2 were stable for more than 12 weeks, while the remaining 5 patients showed progression at 12 weeks. Stoliar and Albert (1974) reported that 7 of 18 patients who had previously failed hormonal manipulation responded to Flutamide treatment.

Gynaecomastia and breast tenderness were seen in both groups of patients, but nausea and vomiting were more common in those who had failed conventional hormonal treatment. Gynaecomastia and breast tenderness have also been reported by other investigators.

Flutamide cannot be considered an ideal drug for the treatment of metastatic carcinoma of the prostate but it may be as effective as stilboestrol for the treatment of this stage of the disease. In cases where stilboestrol cannot be used for fear of thromboembolic phenomena, Flutamide may be considered as an alternative treatment.

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Osteitis Pubis: Treatment by Heparinisation

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Summary—Three cases of osteitis pubis following prostatectomy, herniorrhaphy and combined prostatectomy and herniorrhaphy are presented.

Each case was successfully treated by intravenous heparin after other treatments had failed.

Osteitis pubis is relatively rare, but when encountered it still incapacitates the patient for a period of weeks or months. Various forms of treatment have been proposed, all of which have claimed to improve the condition dramatically. Three cases treated by heparinisation are reported.

Case Reports

Case 1. A 63-year-old man was admitted with urinary retention. Physical examination revealed an enlarged prostate and a right inguinal hernia. Laboratory examinations were normal except for a urinary infection by *Proteus*. A suprapubic prostatectomy and right herniorrhaphy were performed simultaneously. The patient was febrile after the operation and the prostatectomy wound became infected with *Pseudomonas aeruginosa*. The urethral catheter was removed on the sixth day and he was discharged on the fourteenth day post-operatively.

Soon after discharge he began to limp and needed increasing doses of analgesics. Three months later he was admitted to an orthopaedic ward. The wounds were healed. Urine culture was sterile but the erythrocyte sedimentation rate (ESR) was moderately raised. X-rays showed that the pubis was still normal (Figs. a and b). Indomethacin was administered for a week and he was instructed to follow the same treatment as an out-patient.

Because the pain and gait worsened he was readmitted to the urological ward 5 months after operation with a diagnosis of osteitis pubis. This time the pubic bones showed diastasis and destruction of the margins of the symphysis (Fig. c). The ESR was again raised and he was treated with corticosteroids 15 mg per day as well as streptokinase and oxyphenbutazone. For 3 more weeks he was bedridden and unable to flex his thighs. He was then heparinised intravenously—15,000 units initially followed by 10,000 units every 6 h, occasionally alternated with 7500 units according to the prothrombin time.

Improvement was dramatic. The patient was discharged after a week's treatment, walking freely and painlessly. He continued on anticoagulant therapy orally (coumadin) for another month. The ESR had returned to normal at the time of discharge. X-rays taken 6 months later showed sclerosis of the symphysis pubis and the beginning of bone bridging over the gap (Fig. d).

Case 2. A 76-year-old man suffering from myelofibrosis for several years had an urgent prostatectomy in another hospital because of severe haematuria. A stormy post-operative period necessitated hospitalisation for more than 2 months. On returning home he could hardly walk because of pain in the pubic area. A few months later the diagnosis of osteitis pubis was made and he was put on corticosteroids. Nine months after his prostatectomy the patient was admitted to our urological ward for assessment.

He could move around only with the aid of a stick. The pubic bone was tender and movements of the thigh were painful. A large spleen was palpable, filling the flank. All laboratory analyses were within normal limits except for a raised ESR and a leukocytosis (49,400 mm^3) with a shift to the left and many young forms (promyelocytes, metamyelocytes and myelocytes).

A haematological assessment confirmed the diagnosis of myelofibrosis. Since there was no haematological contraindication the patient was heparinised intravenously for 10 days and the improvement was rapid. No bleeding problems were encountered and when discharged he was able to walk easily.

Case 3. A male, 44 years old, had had a herniorrhaphy 45 days before admission. An orchiectomy was done a short while later, probably because of secondary infection. At that time he had suffered from severe and worsening pain in the pubic area until he was no longer able to walk. A diagnosis of osteitis pubis was based mainly on (i) the clinical picture, (ii) an accelerated ESR, and (iii) the X-ray image of symphysiolysis and destruction of the upper margin of the pubic bones.

Corticosteroids were given but there was no improvement. He was then heparinised on the schedule already described. Within 48 hours he had improved so much

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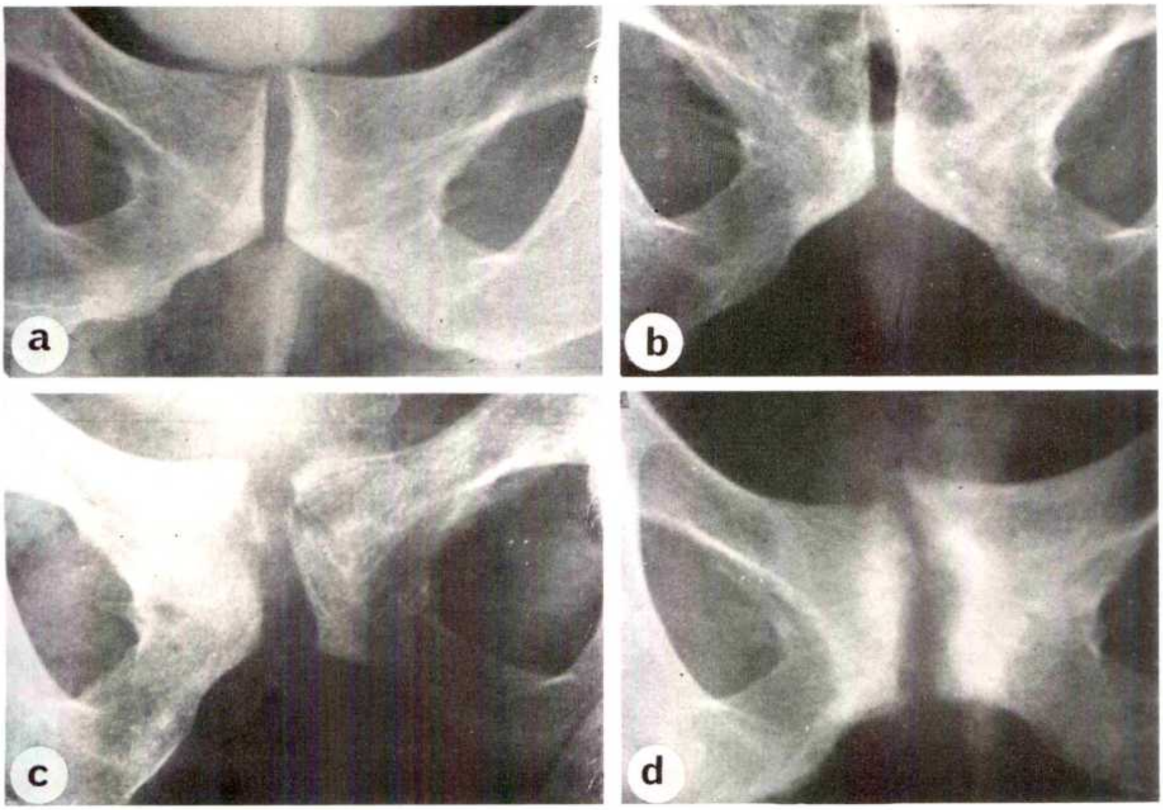

Fig. (a) Normal pubis before operation. (b) After 3 months: some condensation of the borders with only slight symphysiolysis. (c) After 5 months: symphysiolysis and destruction of the margins of the pubic bones, moth-eaten appearance. (d) Fourteen months after operation: new bone formation and bridging of the upper borders.

that he was able to get out of bed and walk about. After a week he was discharged with instructions for further anticoagulant therapy.

Discussion

Since the description of osteitis pubis in 1827 by Elliotson (Barrier *et al.*, 1973) and in 1924 by Edwin Beer (Barzilay *et al.*, 1957), little progress has been made in determining the aetiology of this condition. Factors thought to be associated with its development include trauma, infection, impaired venous circulation to the symphysis (Firstater, 1952; Burns and Gregory, 1977), infective venous thrombosis of the periprostatic venous system (Campbell, 1963) and pubic thrombosis (Mynors, 1974).

Proposed treatments have included antibiotics, analgesics, anti-inflammatory drugs, wedge resection of the pubis (Nanninga and O'Conor, 1976), irradiation, diathermy, vitamin compounds, heat, bed rest, steroids (Thompson and Montie, 1976), oxyphenbutazone (Lapides *et al.*, 1967), and local infiltration with hydrocortisone acetate (Barzilay *et al.*, 1957) or with procaine followed by hydrocortisone (Weiser, 1961). Anticoagulant therapy has been suggested (Barrier *et al.*, 1973; Mynors, 1974) but Barrier used anticoagulants in the belief that there was coexisting thrombophlebitis within the pelvis in 2 patients with post partum osteitis pubis.

In our first case we had tried antibiotics, anti-inflammatory drugs, corticosteroids and bed rest, all without success. In view of Mynors' experience in 1974 we used heparin intravenously and noted a dramatic improvement. Similar results were obtained in the subsequent 2 cases. Heparinisation produced no complications and no further symptoms were noted at follow-up.

We recommend heparinisation as soon as the diagnosis of osteitis pubis is made, in order to prevent unnecessary distress and incapacity.

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Characteristics of the Urethral Pressure Profile in Flaccid Male Paraplegics

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Summary—Several aspects of urethral function were studied in an attempt to identify the factors causing urinary retention in the flaccid paraplegic patient.

The urethral pressure was much higher in all patients at the external sphincter than at the bladder neck. In patients studied sequentially, even from very early following injury, there was little variation in the maximum urethral closure pressure. Radiological studies showed the point of maximal resistance to be distal to the verumontanum. The urethral pressure at this point was largely abolished by phentolamine infusion. There was no variation in the activity of this region with bladder filling or postural change.

It is concluded that in flaccid male paraplegics the major component of urethral resistance is constant, adrenergically innervated muscular resistance in the external sphincter region.

The interplay of factors contributing to urethral resistance is poorly understood. Several components play a part. The following factors may all contribute towards urethral resistance:

1. Smooth muscle at the bladder neck.
2. Extrinsic periurethral musculature (Gosling, 1979).
3. Intrinsic urethral musculature.
4. Total intra-abdominal pressure.
5. Elastic recoil of urethral and periurethral structures (including prostate).
6. Urethral vascular tone.

Any or all of these components could contribute to urethral resistance (and therefore continence) both in the normal male and in the paraplegic. In an attempt to clarify the situation, a detailed study of the urethra in the flaccid male paraplegic was undertaken, on the premise that one of the above components, the extrinsic periurethral musculature, would not be active.

Patients and Methods

Patients

Nine flaccid male paraplegics were chosen for study (Table 1); all had suffered traumatic lesions to the cord. Five were studied during their initial hospitalisation, one was studied 16 years after injury and the remaining 3 patients had undergone removal of the lower cord and conus medullaris from just above the level of a previous injury (cordectomy) because of severe pain. All patients included in the study had clinically complete lesions and no evidence of any reflex activity below the level of the lesion at any stage; specifically, all had absent anal skin and bulbocavernosus reflexes. All had had cystometrograms which showed no evidence of reflex detrusor activity. The accuracy of clinical testing for completeness of a spinal lesion is open to question and it was for this reason that the 3 patients who had undergone cordectomy were included, for in them the level of the neurological lesion was accurately known and there was no question of their lesion being incomplete.

Table 1 Male Flaccid Paraplegics Included in this Study

Patient	*Age*	*Neurological level*	*Diagnosis*	*Period since lesion (or cordectomy)*
B.W.	44	D7	Traumatic paraplegia	9 weeks
K.C.	17	D12	Traumatic paraplegia	5 weeks
R.W.	51	D11	Traumatic paraplegia	9 weeks
G.G.	17	D6	Traumatic paraplegia	23 weeks
C.S.	43	D8	Traumatic paraplegia	16 years
G.T.	34	D12	Traumatic paraplegia	30 hours
D.R.	49	D11	Cordectomy	11 years
T.W.	38	D12	Cordectomy	3 years
D.M.	36	L1	Cordectomy	3 years

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Urethral Pressure Profiles (UPP)

Measurements were made according to the method of Brown and Wickham (1969) using a triple lumen, 10 FG catheter with a radio-opaque marker at the level of the sideholes. Water was infused at 2 ml/min and the catheter was withdrawn slowly using a mechanical puller. Recordings were made with Elkomatic physiological pressure transducers and a Chessel 2-channel chart recorder. During studies of the static urethral pressure profile and of drug effects the second channel was used to record intravesical pressure with 100 ml of fluid in the bladder. From these studies the peak urethral pressures were expressed in terms of cmH_2O above intravesical pressure (maximum urethral closure pressure). The urethral pressure profile was repeated at least 3 times for each study and the result shown is the average of the maximum urethral closure pressures.

Table 2 Maximum Urethral Closure Pressure in each Patient (Average of all Non-medicated readings)

Patient	*Average maximum UPP* (*cmH_2O*)
B W	22
K.C	88
R.W.	40
G.G.	49
C.S	48
G.T.	44
D R.	27
T W	66
D.M.	32

Effect of Posture and Bladder Filling on Urethral Resistance

In these studies the rectal pressure, representing intra-abdominal pressure, was measured and used as the baseline. The initial readings were taken with the bladder empty and the patient supine; the bladder was then filled to 500 ml and the readings repeated. The patient was then propped up with pillows so that the trunk was as near to the vertical as possible and measurements were made with the bladder full and then empty.

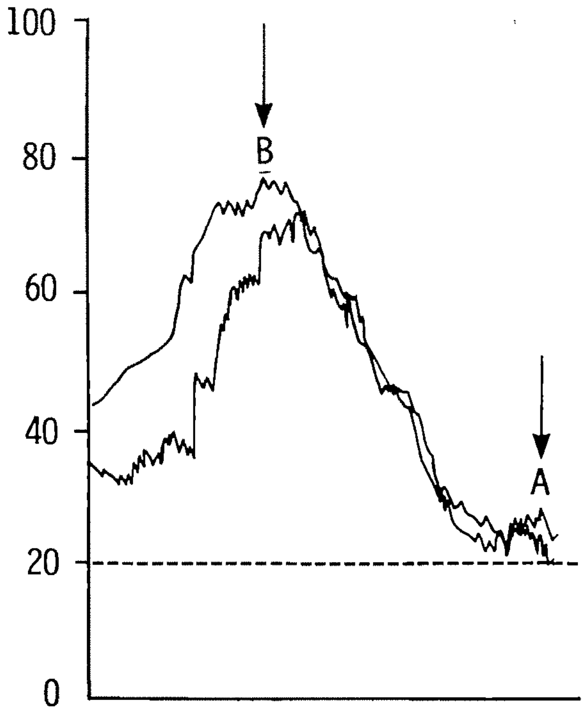

Fig. 1 Two consecutive traces of UPP from the same patient (G.T.) 30 h after injury. Note bladder neck peak (A) and external sphincter peak (B). Dotted line represents intravesical pressure.

Phentolamine Infusion

Each patient was given an infusion of phentolamine on at least one occasion after non-medicated measurements of the maximum urethral closure pressure had been performed. The infusion was given intravenously at a rate of 1 mg per min and, after a period of equilibration, the maximum urethral closure pressure was measured at least twice. The average total dose of phentolamine was 17 mg. Blood pressure was monitored throughout this procedure.

Simultaneous X-ray Studies

The urethral pressure profile was performed as outlined above but with the patient lying in the oblique position on the X-ray table; contrast material was used for all bladder filling and urethral infusion. When the point of maximal urethral closure pressure was reached an X-ray was taken. The procedure was repeated with the bladder full.

Results

Form of the Urethral Pressure Profile

In most patients tested the form of the urethral pressure profile (at 100 ml capacity) was similar to that of the normal male. There was an initial small rise in pressure as the catheter traversed the bladder neck (although less than seen in the normal) and the maximum urethral closure pressure was seen at a lower level in the posterior urethra (Fig. 1). In some patients the peak at the

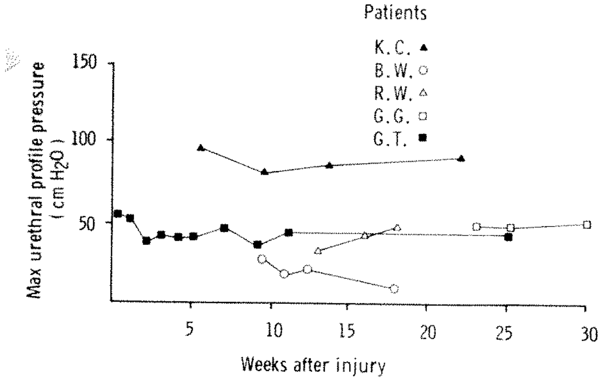

Fig. 2 Change in maximum urethral closure pressure after spinal injury.

bladder neck was not seen at 100 ml bladder capacity and in all patients tested the bladder neck peak was not seen after bladder filling (*i.e.* the bladder neck opened with filling) (Figs. 4 and 5).

Maximal Urethral Closure Pressure

The maximal urethral closure pressure showed a wide range between patients (Table 2) but the results obtained in testing individual patients were relatively constant on repeat testing. There was much less variability of readings in these patients than in spastic paraplegics similarly tested. The numbers of patients involved were not sufficient to establish a correlation between the profile height and either the patient's age or level of his lesion. It was noted, however, that the highest pressure peak was seen in a young patient with a low lesion and the lowest seen in an older patient with a high lesion (Tables 1 and 2).

Table 3 Effect of Phentolamine Infusion on Maximum Urethral Closure Pressure

Patient	*Max. UPP before phentolamine infusion (cmH_2O)*	*Max. UPP during phentolamine infusion (cmH_2O)*	*Fall (%)*
B.W.	17	3	82
K.C.	82	26	69
R.W.	33	7	79
G.G.	49	10	80
C.S.	48	15	69
G.T.	42	13	69
D.R.	27	14	48
T.W.	66	9.5	86
D.M.	32	4	87.5
		Average	74.4

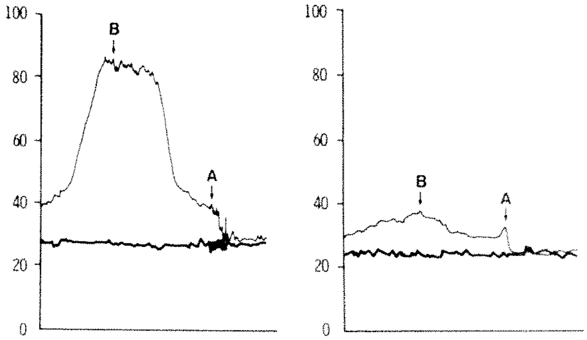

Fig. 3 Urethral pressure profile before (left) and during (right) phentolamine infusion. Note presence of peaks at bladder neck (A) and external sphincter (B). Heavy line represents intravesical pressure.

Sequential Studies

In the 5 patients who were tested following recent injury the studies were repeated on several occasions to follow changes occurring in the early period following spinal lesion. Again the numbers involved were small but there was relatively little change in a particular patient's urethral closure pressure during the early phase (Fig. 2). This was the case particularly in one patient (G.T.) who was first tested at 30 h following injury and in whom there was very little change over the following 5 months.

Phentolamine Infusion

During phentolamine infusion the maximal closure pressure in all patients fell markedly (Table 3), the average reduction being 74.4%. The general form of the profile remained the same and the peak still appeared to be in the lower urethra (Fig. 3). There was no change noted in the baseline (intravesical) pressure during these studies. No patient showed a systolic blood pressure drop of more than 15 mmHg during the procedure.

X-ray Studies

Radiographs were taken in the oblique position at the point of maximum urethral closure pressure in 5 patients. In all patients these pressures were located distal to the verumontanum at the level of the external sphincter (Fig. 4). In most patients the bladder neck was closed at low bladder capacity but opened with filling (Fig. 5), leaving the urethral pressure unchanged (see below).

Changes with Posture and Bladder Filling

Four patients were studied in this way. It was

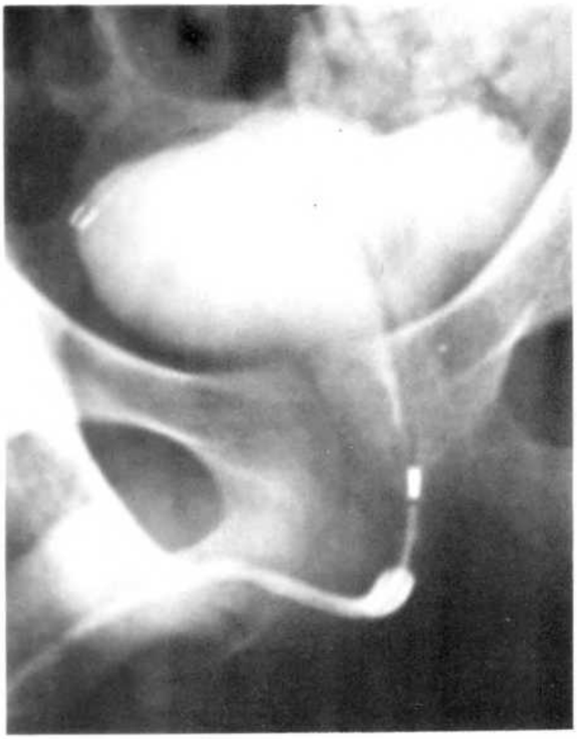

Fig. 4 X-ray marker at point of maximum urethral resistance: 100 ml bladder capacity.

noted that the rectal pressure and the peak urethral profile pressure rose slightly with filling but to a much smaller extent than the intravesical pressure. When the rectal pressure was taken as a baseline there was very little change noted in the maximum urethral pressure in any patient (Table 4). Similarly, with changes in posture all 3 parameters rose by approximately the same amount.

Discussion

It has been previously reported (Abel *et al.*, 1974) that most of the urethral resistance in the flaccid paraplegic is at the external sphincter level. It is of interest to note how little contribution is made by the bladder neck in these patients; although it is closed when the bladder is empty it is open when the bladder is full. Any activity at the bladder neck must be quite weak, as it seems to be easily pulled open by bladder filling.

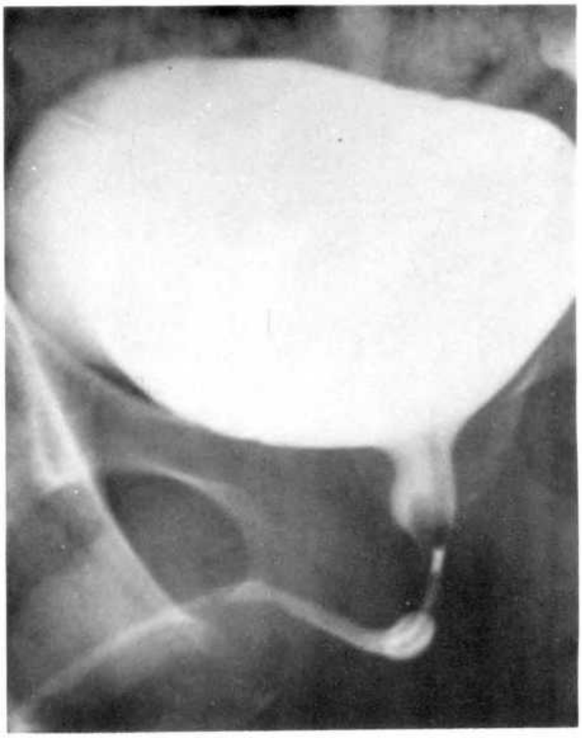

Fig. 5 Same patient with full bladder. Marker at point of maximum urethral resistance. Bladder neck is open. Note incidental vesicoureteric reflux.

We were unable to show any variation of the maximum urethral pressure with bladder filling or change in posture. Although Sunder *et al.* (1978) reported a change in urethral closure pressure in patients who were apparently flaccid paraplegics, this difference was probably due to a raised intravesical pressure when the bladder was full. We were unable to find any evidence of local reflex changes in distal urethral activity due to

Table 4 Findings in Patient (R.W.) with Bladder Filling and Change of Posture

	Intravesical pressure (cmH_2O)	*Rectal pressure (cmH_2O)*	*Maximal UPP (cmH_2O)*	*Change in bladder pressure minus change in rectal pressure*	*Change in maximal UPP minus change in rectal pressure*
Empty supine	16	1	64		
Full supine	30	2	65	+13	0
Empty erect	23.5	7	73	+1.5	+3
Full erect	35	8	69	+12	−2

bladder filling or change in posture. The rise in maximum urethral pressure with a change to the upright position is apparently due to a concomitant rise in intra-abdominal pressure.

The fall in urethral closure pressure with phentolamine infusion (74.4%) seen in our patients was greater than that reported in flaccid paraplegics by Sunder *et al.* (1978) or by Awad *et al.* (1977) for a group of patients in spinal shock. These changes may be due to differences in total dose and mode of administration as well as the probable activity of the extrinsic periurethral musculature during spinal shock in the latter report. It is interesting to speculate how much greater would have been the fall if even larger doses of phentolamine had been used, but it appears that at least the major component of the urethral resistance in these patients can be overcome by alpha blockade. That this effect may be due to decreased vascular tone seems unlikely in view of the minimal fall noted in the systemic arterial pressure and it is generally felt that this mechanism is not of major importance in the normal urethra (Donker *et al.*, 1972).

The effect of elastic recoil in the distal urethra cannot be excluded by our studies, but it could be only a minor component contributing less than 25% of the total urethral closure pressure.

Origin of Activity

On the presumption that there is no pelvic floor activity in these flaccid paraplegics, the urethral activity would appear to reside in the intrinsic urethral musculature at the level of the external sphincter. Gosling (1979) describes this area as slow twitch striated musculature, innervated via the pelvic nerves. Adrenergic nerve endings have not been satisfactorily demonstrated in this area, whereas cholinergic endings are seen (Gosling, 1979; personal communication). This suggests that the effect of alpha-adrenergic blockade may be at the level of the pelvic plexus, via a mechanism similar to that postulated by Elbadawi and Schenk (1971). Whether we are blocking circulating catecholamines or sympathetic nervous system activity with phentolamine cannot be determined from our studies, but a study of a larger number of patients and a correlation of the urethral pressure with the level of the lesion (*i.e.* above or below the level of reported sympathetic outflow) might help to answer this question.

Application to the Normal Patient

That the maximum urethral closure pressure varies little during the early period following injury to the lower cord or roots suggests that the musculature involved does not undergo compensatory hypertrophy due to denervation supersensitivity and is, in fact, probably active to about the same degree in the neurologically intact patient and probably represents a major continence mechanism in patients with an incompetent bladder neck.

It is concluded that the major component of urethral resistance in the flaccid male paraplegic appears to be due to the distal intrinsic urethral sphincter. This muscle is under adrenergic control and does not appear to be affected by bladder filling or change in posture.

Acknowledgement

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Non-seminoma Germ Cell Tumours (Malignant Teratoma) of the Testis

Results of Treatment and an Analysis of Prognostic Factors*

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Summary—The results of treatment of 126 patients with non-seminoma germ cell tumours (malignant teratoma) of the testis are presented. Of this group 81% are alive and 70% disease-free. Of 98 patients who had had no prior treatment 83% are alive and 76.5% disease-free. Of 43 early-stage patients 41 (95%) are alive and tumour-free despite a 21% relapse rate after radiotherapy.

The disease-free rate in patients with advanced disease treated with chemotherapy, and in some cases radiotherapy and/or surgery, ranged from 100 to 9% and was strongly dependent upon the volume of metastatic tumour and the histology. Patients with malignant teratoma undifferentiated (embryonal carcinoma) showed a significantly higher disease-free survival rate than those with malignant teratoma intermediate (teratocarcinoma). Twenty-six men with advanced disease received radiotherapy after chemotherapy and of these 23 (88%) are alive and 21 (81%) are disease-free. No difference in disease-free survival rate was seen between advanced-stage patients receiving vinblastine and bleomycin and those receiving, in addition, cis-platinum. The overall drug-related mortality was 4.5%.

Serum alpha-fetoprotein (AFP) and beta-human chorionic gonadotrophin (ß-HCG) levels were valuable monitors in advanced disease but not prognostically significant if allowance was made for tumour volume. Fifteen patients had surgical resection of residual masses and one died post-operatively.

The prognosis of patients with metastatic non-seminoma germ cell tumours (malignant teratoma) of the testis has been profoundly modified by the development of more effective chemotherapy (Samuels *et al.*, 1975, 1976; Einhorn and Donohue, 1977, 1979). In previous publications we have reported our experience in the management of malignant teratoma of the testis before (Smithers *et al.*, 1971; Peckham and McElwain, 1975; Peckham *et al.*, 1977) and after the introduction of effective chemotherapy (Peckham *et al.*, 1979). In a retrospective analysis of patients treated by irradiation for retroperitoneal lymph node metastases, attention was drawn to the influence of tumour volume on treatment outcome (Tyrrell and Peckham, 1976). Subsequent observations have shown that chemotherapeutic response is similarly influenced by tumour volume (Samuels *et al.*, 1976; Einhorn and Donohue, 1977) and it was suggested that irradiation of initial disease sites following chemotherapy might be advantageous in selected patients with advanced disease (Peckham *et al.*, 1977, 1979). At the same time, elective lymph node irradiation for patients with early-stage disease, with deferral of chemotherapy until relapse occurred, was shown to be a practicable and successful treatment policy.

In more recent studies attention has been paid to the identification of important prognostic factors so that treatment may be adjusted more precisely to the patient's needs. As a result of an analysis of serum tumour markers in patients with clinical Stage I disease (Raghavan *et al.*, 1981) and an appreciation of the role of computed axial tomography (CAT) (Husband *et al.*, 1981), a study has been started in which selected patients receive no elective treatment other than orchiectomy and are closely monitored for evi-

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* The contents of this paper formed the basis of the Legg Memorial Lecture given at King's College Hospital, London, on 27 May 1980 by M.J.P.

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dence of metastatic tumour. In advanced disease, therapeutic outcome has been considered in relation to tumour volume and histology and to serum alpha-fetoprotein and beta-human chorionic gonadotrophin levels.

Patients and Methods

One hundred and twenty-eight patients with testicular teratoma were referred for treatment between December 1975 and April 1979. Two patients were lost to follow-up (both Stage I, one MTU, one MTI) and 126 were available for analysis. Of the total group, 43 had early-stage disease (I, IIA) and 88 advanced disease. Ninety-eight patients (all early-stage patients and 55 advanced-stage patients) had had no previous therapy, whereas 33 patients with advanced disease had had previous irradiation. Five early-stage patients who were irradiated by us and who relapsed are also included in the analysis of previously treated advanced-stage disease.

Histology As much of the primary tumour as possible was obtained and examined in all patients. Patients were classified according to the criteria of the British Testicular Tumour Panel (Pugh, 1976) into malignant teratoma differentiated (MTD), malignant teratoma intermediate (MTI), malignant teratoma undifferentiated (MTU) or malignant teratoma trophoblastic (MTT). The presence of associated seminoma or yolk sac components was noted but did not modify the classification.

Staging Methodology The following investigations were performed: lymphography, chest radiography and whole lung tomography, intravenous urography, renal and hepatic function tests and full blood count. The liver and retroperitoneum were ultrasonically scanned until CAT scanning became available in mid-1977. Since then all patients have had CAT scans of the liver, retroperitoneum and lungs unless obvious metastatic disease rendered this unnecessary.

All patients had sequential serum sampling for AFP and ß-HCG levels from the time of presentation.

Staging Classification This describes the extent of the tumour, the site(s) of involvement and the tumour volume.

I Lymphogram negative, no evidence of metastases.

II Lymphogram positive, metastases confined to abdominal nodes, 3 subgroups are recognised:
  A. Maximum diameter of metastases <2 cm.
  B. Maximum diameter of metastases 2-5 cm.
  C. Maximum diameter of metastases >5 cm.

III Involvement of supradiaphragmatic and infradiaphragmatic lymph nodes. No extralymphatic metastases.
  Abdominal status:
  A, B, C as for Stage II.

IV Extralymphatic metastases.
  Suffixes as follows:
  0—lymphogram negative,
  A, B, C as for Stage II.
  Lung status:
  $L_1 < 3$ metastases.
  L_2 multiple metastases, none exceeding 2 cm maximum diameter.
  L_3 multiple metastases, one or more exceeding 2 cm diameter.
  *Liver status:**
  H_+ = liver involvement.
  * *Criteria for liver involvement*
  Of the 4 following parameters, 3 should be positive before liver involvement is diagnosed.

1. Abnormal liver function tests.
2. Positive CT scan.
3. Positive ultrasonic or isotopic scan.
4. Clinical enlargement.

Treatment Protocols

Stage I Although, at present, selected Stage I patients receive no treatment other than orchiectomy (see Discussion), all patients with clinical Stage I disease in the present series received lymph node irradiation. Treatment to the para-aortic and ipsilateral pelvic nodes was given by anterior and posterior fields extending from D10/11 to the obturator foramen and extending laterally to the renal hila. A mid-plane dose of 40 Gray in 20 fractions over 4 weeks was employed. The inguinal nodes and scrotal sac were irradiated only if there had been scrotal interference or scrotal involvement by tumour. If there had been a previous orchiopexy the inguinal nodes were irradiated.

Stage IIA The approach described above was used. If it was considered technically feasible, a supplementary dose of 5 to 10 Gray was given to the involved nodes by smaller fields. Initially, one month following abdominal node irradiation, the mediastinum and supraclavicular fossae were irradiated. However, supradiaphragmatic irradiation was abandoned since it renders subsequent chemotherapy hazardous.

Stage IIB, IIC, III, IV 0-C L_1 L_2 (Advanced-Stage Group 1) Patients in these categories, collectively designated as Advanced-Stage Group (ASG 1), either had no detectable extralymphatic metastases or lung metastases limited in number and size. The initial treat-

Table 1 Chemotherapy for Advanced NSGCT* Testis (Royal Marsden Hospital 1976-1979)

Regime	*Number of patients*		*Number of courses*	*Average*
VB	47		1-6	3.6
PVB	16		1-6	3.8
PVB + VB	25	PVB	1-6	2.8
		VB	1-5	2.3

VB = vinblastine, bleomycin.
P = cis-platinum.
* NSGCT = non-seminomatous germ cell tumour.

ment was chemotherapy. Between December 1975 and January 1978 a combination of vinblastine and bleomycin (VB) (Samuels *et al.*, 1975, 1976) was employed and subsequently a 3-drug regime comprising cis-diamminedichloroplatinum 11, vinblastine and bleomycin (PVB) (Einhorn and Donohue, 1977, 1979). In the VB regime, vinblastine 15 mg/m^2 was given intravenously on days 1 and 2 and bleomycin 30 mg daily by continuous intravenous infusion on days 1 to 5. Courses were given at intervals of 3 to 4 weeks. In the PVB regime, cis-platinum 20 mg/m^2 was given intravenously daily on days 1 to 5, preceded by intravenous hydration to maintain a high urine output. Bleomycin, 30 mg intravenously, was given on days 2, 9 and 16 and vinblastine, initially in a dose of 0.2 mg/kg and subsequently 0.15 mg/kg, intravenously on days 1 and 2. Courses were given at 3-weekly intervals. The number of courses varied both by design and because of toxicity. Initially 2 courses, and subsequently 4 to 6 courses, of VB were given. A minimum of 4 courses of PVB was aimed at. Renal function was monitored throughout treatment. As shown in Table 1, 47 patients received VB only, 16 PVB and 25 both PVB and VB (this latter group was treated in the period of changeover between the 2 regimes). The number of courses and average given are shown.

If serum markers were normal and there was no evidence of disease progression, radiotherapy was given to sites of initial disease (excluding the lungs). A minimum interval of 4 weeks elapsed between the end of chemotherapy and the start of radiotherapy. The minimum tumour dose was 40 Gray in 4 to 5 weeks and if practicable a boost dose of 5 to 10 Gray was delivered by smaller fields. In some patients with very bulky disease, in whom partial and continuing regression was evident after 4 courses, a further 2 courses of chemotherapy were given. Conversely, if massive disease showed little evidence of response and radiotherapy was technically difficult, the patients proceeded directly to surgery. Those patients receiving radiotherapy were reassessed 4 to 6 weeks after treatment. If a residual abnormality was demonstrable on a CAT scan the patient was explored and the mass excised for histological examination (Hendry *et al.*, 1980).

Data Analysis The standard actuarial method (life-table analysis) was employed. The survival rates given are for disease-free survivors and are observed and minimum rates, accounting for all deaths, regardless of cause. Survival times were calculated from the date of initiation of therapy. Greenwood's (Greenwood, 1926) method for calculating the standard error of the survival rate was used and consequently the standard errors of rates based on small numbers of cases must be treated with caution. In comparing pairs of survival rates, the difference of the rates was divided by the standard error of their difference and the result referred to the normal distribution.

Results

(a) Early-stage Disease (Table 2) Of 43 Stage I and IIA patients 41 (95%) are disease-free despite

Table 2 Outcome of Treatment in 98 Patients With Previously Untreated NSGCT* Testis (Royal Marsden Hospital 1976-1979)

Stage	*Total patients*	*Relapsed*	*Disease-free*	*Alive with disease*	*Dead of disease*	*Dead of intercurrent disease or treatment*
I	39	8	37 (95%)	—	—	2
IIA	4	1	4 (100%)	—	—	—
IIB-III	17	1	13 (76.5%)	2	1	1
IVO A L_1 L_2	9	—	9 (100%)	—	—	—
IVB C L_1 L_2	10	—	6 (60%)	2	1	1
IVO A L_3	8	—	5 (62.5%)	—	3	—
IVB C L_3	5	—	1 (9%)	2	2	—
IV H +	6	—		—	6	—
Total	98	10	75 (76.5%)	6	13	4

* NSGCT = non-seminomatous germ cell tumour.

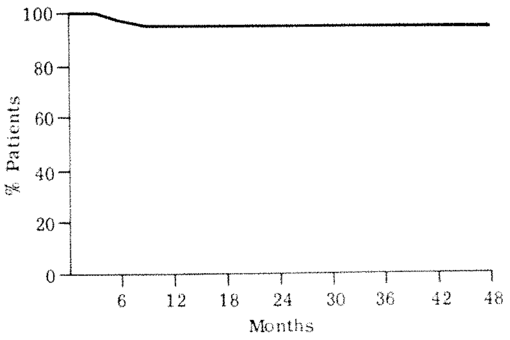

Fig. 1 Stage I and IIA non-seminomatous germ cell tumours of the testis: disease-free survival (43 patients) (Royal Marsden Hospital 1976-1979).

a relapse rate of 21% after radiotherapy. One patient died of gastrointestinal haemorrhage while on chemotherapy and the second, an elderly man, died of an apparently unrelated cerebrovascular accident 15 months after treatment. The latter patient was disease-free. Figure 1 shows the disease-free survival curve for the Stage I and IIA patients.

(b) Advanced-stage Patients The results showed that substage based upon tumour bulk was of prognostic significance. Thus the disease-free rate within Stage IV ranges from 100 to 9% (Table 2). The disease-free survival curves for the substage groups are shown in Figure 2. The following differences are significant at one year.

IV O A L_1 L_2>IV B C L_1 L_2 ($P<0.05$).
IV O A L_1 L_2>IV B C L_3 H+ ($P<0.05$).
II III>IV B C L_2 H+ ($P<0.001$).
IV B C L_1 L_2>IV B C L_3 H+ ($P = 0.05$).
IV O A L_3>IV B C L_3 H+ ($P = 0.005$).

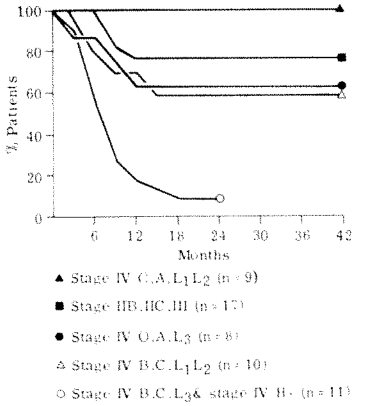

Fig. 2 Previously untreated advanced non-seminomatous germ cell tumours of the testis: disease-free survival by stage (Royal Marsden Hospital 1976-1979).

A similar trend was seen in previously treated patients (Table 3). It was of interest that bulky pulmonary metastases alone (IV O A L_3) were not associated with as sinister a prognosis as was the association of bulky abdominal and pulmonary disease (IV B C L_3).

Influence of Prior Irradiation Previously untreated advanced-stage patients showed a better disease-free survival rate than previously irradiated patients (Fig. 3), but the difference was not significant. If prior treatment status was examined by advanced-stage subgroup no difference was observed in ASG II patients, whereas a difference was seen in ASG I (Fig. 4) ($P = 0.07$).

Serum AFP and β-HCG and Results of Treatment

(i) Presence or Absence of Elevated Serum AFP and β-HCG Levels There is a clear relationship between tumour bulk and elevated serum marker levels (Table 4). Thus in Stage IV patients with

Table 3 Chemotherapy For Patients With NSGCT* Testis Relapsing After Radiation Therapy: Outcome of Treatment by Stage (Royal Marsden Hospital 1976-1979)

Stage†	*Total patients*	*Disease-free*	*Alive with disease*	*Dead of tumour*	*Dead of intercurrent disease*
IIB CIII	9	4 (44%)	2	2	1
IVO A L_1L_2	11	7 (64%)	3	—	1
IV B C L_1L_2	5	2 (40%)	2	1	—
IV O A L_3	5	2 (40%)	1	1	1
IV B C L_3 H+	3	0 (0)	—	2	1
Total	33	15 (45.5%)	8 (24.2%)	6 (18.2%)	4 (12.1%)

* NSGCT = non-seminomatous germ cell tumour.
† Represents stage at time of initiation of chemotherapy.

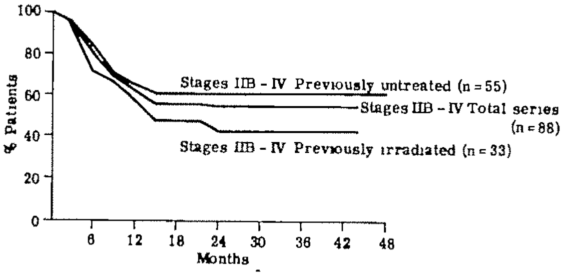

Fig. 3 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival (Royal Marsden Hospital 1976-1979)

small-volume disease (IV O A L_1L_2), 55% showed no elevation of AFP or ß-HCG. In contrast, in patients with bulky Stage IV (IV B C L_3 H+), 72% had elevation of both AFP and ß-HCG. The disease-free survival of marker-negative patients was not significantly better than that of patients with elevation of one or both markers (Fig. 5). Indeed, in patients with small-volume Stage IV disease and positive markers, the disease-free survival rate was superior to that observed in the marker-negative group, although the difference was not significant (Fig. 6).

(ii) Levels of AFP and β-HCG in the Serum

Figure 7a shows disease-free survival rates for advanced-stage patients according to the titre of AFP and ß-HCG in the serum. The downward trend agrees with the observation that high marker levels tend to be associated with bulky disease which in turn influences therapeutic outcome. In Figures 7b and 7c an attempt is made to examine the disease-free rate by serum marker levels of AFP and ß-HCG within each individual staging category. The numbers are too small to permit detailed analysis but suggest that, after correcting for tumour bulk, high marker levels *per se* were not prognostically significant.

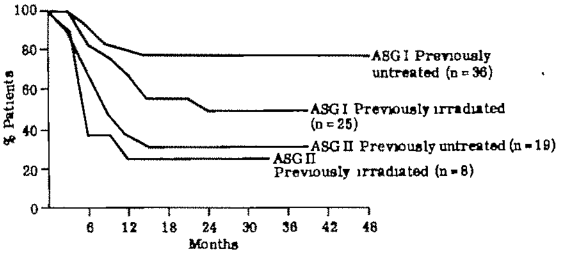

Fig. 4 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by prior treatment status (Royal Marsden Hospital 1976-1979).

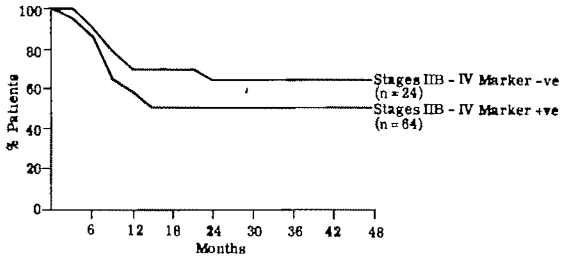

Fig. 5 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by serum marker status (Royal Marsden Hospital 1976-1979).

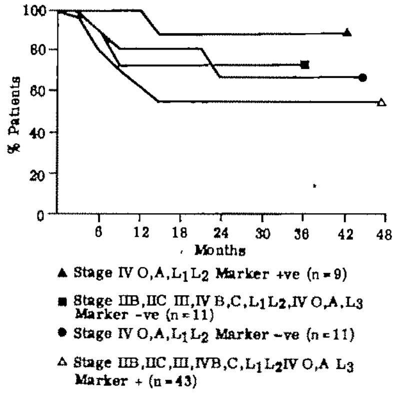

Fig. 6 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by stage grouping and serum marker status (Royal Marsden Hospital 1976-1979).

Table 4 Serum Marker Status in Advanced NSGCT* Testis in Relation to Bulk of Disease (Royal Marsden Hospital 1976-1979)

	Both normal	*Both elevated*	*AFP elevated only*	*HCG elevated only*
IV O A L_1 L_2	11 (55%)	0	4 (20%)	5 (25%)
II III IV B C L_1L_2	9 (22%)	17 (41%)	10 (24%)	5 (12%)
IV O A L_3	3 (23%)	4 (31%)	3 (23%)	3 (23%)
IV B C L_3 H+	2 (14%)	10 (72%)	2 (14%)	0

* NSGCT = non-seminomatous germ cell tumour.

Table 5 Advanced NSGCT* Testis: Initial Marker Status and Marker Pattern on Relapse (Royal Marsden Hospital 1976-1979)

Marker status at time of starting chemotherapy				*Outcome of treatment*				
				NED	*Relapse*			
AFP		*HCG*			*Marker +*		*Marker −*	
+	−	+	−		*AFP*	*HCG*	*AFP*	*HCG*
	36			27	2		7	
39†				20	11		8	
			44	26		1		17
		37		23		8		6

* NSGCT = non-seminomatous germ cell tumour.
† Number of patients.

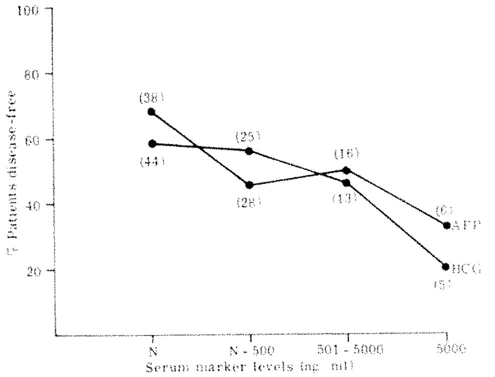

Fig. 7a Advanced non-seminomatous germ cell tumours of the testis: disease-free survival and serum levels of alpha-fetoprotein (AFP) and ß-human chorionic gonadotrophin (ß-HCG). Numbers in parentheses = total number of patients at risk.

(iii) Serum Marker Status Prior to Treatment and at Relapse (Table 5) Of 36 patients with advanced disease who were initially AFP-negative, 2 of 9 relapses were associated with elevated serum AFP levels; one of the 18 initially ß-HCG-negative patients who relapsed had elevated serum ß-HCG levels; 8 of the 19 relapses in patients with initial elevation of serum AFP had normal serum AFP levels; 6 of the 14 relapses in ß-HCG-positive patients were associated with normal ß-HCG serum levels.

Histology

(i) Early-stage Disease (Table 6) Twenty-nine of the 43 Stage I and IIA patients had an MTI primary tumour and 6 (20%) relapsed; 9 had an MTU tumour and 2 (22%) relapsed.

(ii) Advanced-stage Disease (Table 7) The disease-free rate was significantly better for patients with MTU than MTI (Fig. 8) ($P = 0.01$). The difference was due to the ASG I patients in whom the MTU group showed a significantly superior survival ($P = <0.05$). No difference was seen in the ASG II group (Fig. 9). Too few MTT patients were available for analysis.

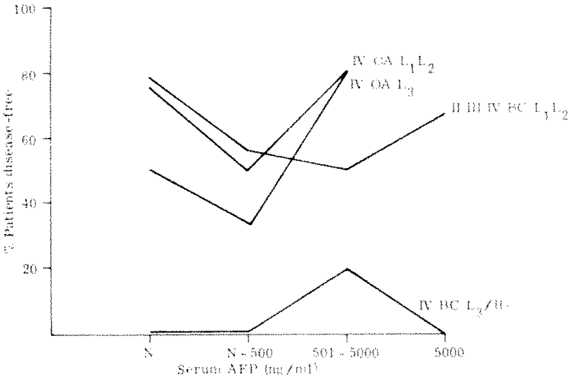

Fig. 7b Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by stage category in relation to serum AFP level.

Table 6 Early Stage Malignant NSGCT* Testis Receiving Orchiectomy, Lymph Node Irradiation and Chemotherapy for Relapse. Outcome by Histology (Royal Marsden Hospital 1976-1979)

Stage	*Histology*	*Total patients*	*Relapses*	*Currently disease-free*	*Dead of tumour*	*Dead of inter-current disease*
I	MTD	1	—	1	—	—
I	MTI	29	6	28	—	1
I	MTU	9	2	8	—	1
IIA	MTI	2	1	2	—	—
IIA	MTU	2	—	2	—	—
Total		43	9	41 (95.3%)	—	2

* NSGCT = non-seminomatous germ cell tumour.

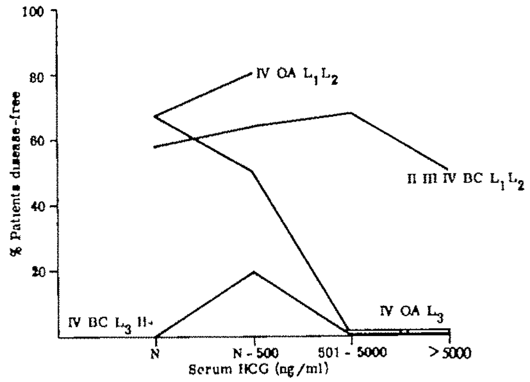

Fig. 7c Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by stage category in relation to serum HCG level.

Type of Chemotherapy and Treatment Outcome The VB and PVB regimes have been used sequentially and a formal comparison cannot be made. However, the use of PVB alone or in conjunction with VB was not associated with a higher disease-free survival rate in any category within the advanced-stage groups (Table 8).

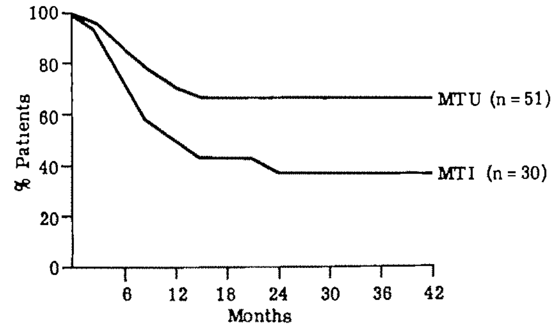

Fig. 8 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by histology (Royal Marsden Hospital 1976-1979).

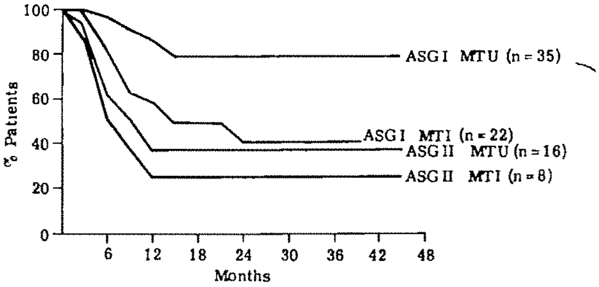

Fig. 9 Advanced non-seminomatous germ cell tumours of the testis: disease-free survival by stage and histology (Royal Marsden Hospital 1976-1979).

Radiotherapy to Initial Disease After Chemotherapy Only patients who had had no previous irradiation and who were included in the ASG I group were eligible for post-chemotherapy irradiation. Of 36 eligible patients 26 were irradiated. Radiotherapy was not employed in the remaining 10 either because the disease progressed on chemotherapy or because we decided to operate and remove bulky residual tumour. Of 26 men who were irradiated 23 (88.4%) are alive and 21 (80.8%) are disease-free. Two patients died as a result of their tumour and one died post-operatively. Patients have been followed up for between 12 and 45 months since the start of treatment (median 32.5 months). Of those patients who did not receive radiotherapy either because they proceeded directly to surgery (10) or because they had been previously irradiated (25), 19 (54.3%) are disease-free.

Selected patients who had completed chemotherapy and radiotherapy proceeded to surgery, but 14 received only chemotherapy and radiotherapy; of these, 12 (85.7%) are disease-free.

Surgery A total of 15 patients underwent surgical resection of residual masses in the retroperitoneum (14) or thorax (1) (Table 9). Eleven patients had had previous irradiation and 9 showed no histological evidence of malignancy. Of these 15 patients, 12 (80%) are disease-free compared with 16 out of 21 (76.2%) ASG I patients who were eligible for surgery but who did not receive it. In all, 11 men who underwent surgery had negative histology and 9 (81.8%) are disease-free. Four men had positive histology and 3 of these remain free from recurrent tumour.

Table 7 Disease-free Survival in Advanced NSGCT* Testis by Substage and Histology (Royal Marsden Hospital 1976-1979)

Stage	*Histology*			
	MTI	*MTU*	*MTT*	*YS*
ASG I†	10/22‡	28/35	3/9	
ASG II	2/8	6/16	6/2	0/1
Overall	12/30 (40%)	34/51 (66.7%)	3/6 (50%)	0/1

* NSGCT = non-seminomatous germ cell tumour.
† ASG = advanced stage group (see text).
‡ Number disease-free/total patients.
MTI = malignant teratoma intermediate.
MTU = malignant teratoma undifferentiated.
MTT = malignant teratoma trophoblastic.
YS = yolk sac carcinoma.

Table 8 Outcome of Treatment for Advanced NSGCT* Testis by Type of Chemotherapy (Royal Marsden Hospital 1976-1979)

Stage	*Chemo-therapy*	*Total patients*	*Number disease-free*	*(%)*
II III IV B C L_1 L_2	VB	20	13	65
	PVB ± VB	20	12	60
IV O A L_1 L_2	VB	13	11	84.6
	PVB ± VB	8	5	62.5
IV L_3 H +	VB	14	5	35.7
	PVB ± VB	13	3	23.1

* NSGCT = non-seminomatous germ cell tumour.

Table 9 Advanced NSGCT* Testis: Excision of Residual Retroperitoneal Masses After Chemotherapy ± Radiotherapy (Royal Marsden Hospital 1976-1979)

Treatment	*Total patients*	*Histology of resected material*		
		Nega-tive	*Differ-entiated*	*Tumour present*
Chemotherapy-radiotherapy	11	8	1	2
Chemotherapy	4	1	1	2

* NSGCT = non-seminomatous germ cell tumour.

Treatment-related Deaths There were 4 chemotherapy-related deaths and one post-operative death (Table 10). The overall drug-related mortality was 4.5% and was higher in previously irradiated patients (9%) than in patients who had had no previous treatment (1.8%). Of the 3 patients who died, 2 had had infradiaphragmatic and supradiaphragmatic irradiation.

Discussion

The present report confirms earlier observations (Peckham *et al.*, 1979) that abdominal node irradiation and chemotherapy for relapsed clinical Stage I teratoma testis can be effective. However, advances in non-invasive staging methods may make it possible to distinguish patients who can be cured by orchiectomy alone from those with a high risk of occult extralymphatic metastases. In studying the role of CAT scanning in 80 patients with previously untreated disease we found that 4 out of 21 patients placed in Stage I after conventional staging had small pulmonary metastases (Husband *et al.*, 1981).

In a recent analysis of serum AFP and ß-HCG levels measured after orchiectomy and before radiotherapy we found that out of 48 patients who either had persistently negative marker levels or who showed rapid clearance after orchiectomy, only 7 (14.6%) subsequently relapsed, whereas of 11 patients where there was a slow or incomplete fall of elevated serum marker levels prior to irradiation, 7 (63.6%) relapsed after radiotherapy ($P = 0.01$).

On the basis of these observations, it is now our policy not to treat further Stage I patients who are CAT scan negative and in whom serum markers are either persistently negative or fall promptly after orchiectomy, a policy made feasible by the effectiveness of chemotherapy in small volume disease.

Table 10 Advanced NSGCT* Testis: Treatment—Related Deaths (Royal Marsden Hospital 1976-1979)

Stage		*Chemotherapy (number of courses)*		*Time following start of chemo-therapy to death (months)*	*Cause of death*
		VB	*PVB*		
Not irradiated previously	II	1	3	8	Post-operative
	IV A L_3	1		1	Chemotherapy
Previously irradiated	IV O L_1	2		2	Chemotherapy
	IV O L_3	2	4	5	Chemotherapy
	IV H +		1	1	Chemotherapy
Total deaths from chemotherapy	4/88 = 4.5%				
Total deaths from previously untreated group	1/55 = 1.8%				
Total deaths from previously irradiated group	3/33 = 9.0%				

* NSGCT = non-seminomatous germ cell tumour.

Excellent results have also been reported in early-stage disease with radical node dissection and chemotherapy for early relapse (Donohue *et al.*, 1978; Fraley *et al.*, 1979; Williams *et al.*, 1980) or adjuvant chemotherapy (Fraley *et al.*, 1979; Skinner and Scardino, 1979; Vugrin *et al.*, 1979). The optimal treatment approach thus cannot be decided in terms of survival results alone and considerations of intensity of treatment and attendant morbidity, including preservation of sexual function and fertility, are crucially important.

It is anticipated that approximately 75% of Stage I patients in the "watch policy" group may be cured by orchiectomy and that early detection of disease in the remaining 25% will lead to a high probability of curative therapy. Conversely, in patients with apparent Stage I disease who show persistent serum marker elevation after orchiectomy, the fact that more than 50% relapse despite abdominal node irradiation is an indication that this group should receive chemotherapy. The results presented above in small-volume Stage IV disease show that such a policy should be highly successful.

In patients with small abdominal node metastases demonstrated at lymphography (IIA) we have shown previously that the results of radiotherapy are comparable with those obtained in Stage I disease (Tyrrell and Peckham, 1976). These results were obtained by infradiaphragmatic and supradiaphragmatic irradiation and this is hazardous should subsequent chemotherapy be necessary (Peckham *et al.*, 1979). Now we give up to 4 cycles of PVB and then treat the involved nodes by radiotherapy, though the successful use of 2 cycles of PVB in patients with positive nodes on radical node dissection (Williams *et al.*, 1980) suggests that less intensive chemotherapy and local irradiation may be equally successful in clinical Stage IIA disease. Since 1979, patients who relapsed soon after radiotherapy have been treated with a combination of bleomycin, the epipodophyllotoxin VP16-213 and cis-platinum (BEP). This combination has been developed on the basis of the activity of VP16 in non-seminomas (Fitzharris *et al.*, 1980) and the desirability of developing a less toxic drug combination which might eventually be employed in primarily untreated patients with small volume disease. As is the case for clinical Stage I disease, it is clear that either radiation therapy or surgery in conjunction with chemotherapy may give excellent results in patients with abdominal node metastases (Whitmore, 1979). The selection of an optimal treatment policy will depend upon the identification of the deficiencies of each approach in terms of cure and toxicity.

The results obtained in advanced disease demonstrate the important prognostic significance of tumour volume and emphasise the difficulty of comparing the results obtained in different centres unless a detailed statement of the characteristics of the patient population is made. Small volume disease is curable with high probability, whereas the association of bulky abdominal tumour and bulky lung disease remains a formidable therapeutic problem demanding an alternative and improved chemotherapeutic approach.

The contribution of irradiation following chemotherapy cannot be assessed from the present experience and needs to be tested in a controlled clinical trial. We have shown that a sequential drug-radiation approach is feasible and appears, at least in the medium term, not to be associated with unexpected sequelae. The frequency in the present series of histologically-viable tumour in masses resected after chemotherapy and radiotherapy is lower than that reported following chemotherapy alone (Golbey *et al.*, 1979; Einhorn, 1980; Garnick *et al.*, 1980). In these latter reports approximately 35% of patients showed evidence of residual malignancy. In the present series it is also encouraging that the major difference in disease-free survival rates was observed between previously irradiated and untreated patients in the category (ASG I) eligible for radiotherapy following chemotherapy.

Serum AFP and ß-HCG are of considerable prognostic significance in apparent early-stage disease, as indicated above. They are also valuable monitors of disease progress. However, it should be noted that from the present experience approximately 40% of initially marker-positive patients may relapse without marker elevation. Conversely, a proportion of marker-negative patients have elevated serum marker levels on relapse. Thus persistent elevation of serum marker levels is significant, whereas the converse is not always true. It is clear that serum marker levels are related to the volume of metastatic tumour and since, as discussed above, tumour bulk is an important prognostic determinant, serum marker levels, if considered in isolation, are likely to be related to treatment outcome. In the present series, if presence or absence of elevated serum markers is considered within individual stage subgroups, there is no evidence that markers are prognostically significant.

Furthermore, the level of AFP or ß-HCG in the serum does not appear to influence the outcome of treatment, although more data are needed to resolve the latter point. If, for a group of patients with a comparable tumour burden, serum marker levels are not prognostically significant, it would suggest that the AFP and ß-HCG-producing cell populations are not dissimilar in therapeutic sensitivity from the tumour cell population unassociated with marker production. Studies in xenografted human teratomas are in progress in an attempt to resolve this question (Selby *et al.*, 1979; Raghavan *et al.*, 1980).

Although advances in immunocytochemistry have demonstrated clearly the imperfections of classical histopathological classifications (Heyderman, 1979), the presence or absence of evidence of differentiation appears to be of prognostic significance. Thus, in advanced disease, undifferentiated tumours (embryonal carcinomas) show a significantly superior disease-free survival rate compared with intermediate malignant teratoma (teratocarcinoma). Other features, such as prognosis in Stage I (Peckham, 1979), local extension of the primary tumour (Pugh, 1976) and stage distribution (Peckham, 1981) indicate important behavioural differences between MTU and MTI.

Finally, although it is clear that the earlier promise of improved treatment results has been maintained, the toxicity of VB and PVB cannot be over-emphasised. The morbidity of these regimes has been fully described elsewhere (Samuels *et al.*, 1975, 1976; Einhorn and Donohue, 1977, 1979) and although the risk of mortality falls with experience, it is likely to remain an attendant hazard with the corollary that chemotherapy should be employed only when it is clearly essential and by clinicians experienced in its use and in the overall management of this complex group of tumours. The observation that treatment results in the present series were similar for VB and PVB is of interest, since these 2 regimes have not been compared in a controlled clinical trial and the superiority of PVB is generally assumed from results reported from different institutions. As noted above, because of the influence of prognostic factors such as histology and tumour volume, comparison of results using different therapeutic approaches must be treated with caution unless it is clear that different series are comparable in composition.

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The Histopathology of the Epididymis in a Group of Cases of Azoospermia with Normal Testicular Function

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Summary—The histopathology of the head of the epididymis in cases of azoospermia associated with normal testicular function is described. In 2 specimens congenital absence of the vas deferens was associated with stuffing of all of the tubules with normal spermatozoa but no other abnormality. In 30 specimens from cases with idiopathic epididymal obstruction there were abnormalities in the vasa efferentia. These included both extreme narrowing of the lumen due to thickening of the wall by fibrosis and also distension of the lumen by sperm and degenerate debris. Small sperm granulomata were present in the tubular wall in 10 specimens and foreign body granulomata were present in 20 specimens.

It is suggested that either persistent low grade infection, congenital abnormality or acute obstruction due to ischaemic or traumatic damage may be the initial lesion. If the infection or the obstruction is not speedily resolved, the condition may become self-perpetuating.

One of the causes of male infertility is the failure of normally produced spermatozoa to reach the ejaculate. This may be the result of some congenital obstruction to the normal passage of sperm or of acquired obstruction. Acquired obstruction is most likely to occur within the epididymis. Gonorrhoea, tuberculous epididymitis, nonspecific epididymitis and certain surgical procedures such as the repair of hernia or hydrocele are known causes of epididymal obstruction. There remains a group of patients in whom no cause for the obstruction is obvious and they are labelled "idiopathic". Treatment of this latter group by epididymovasostomy has had disappointing results. This paper is part of an investigation into the management of azoospermia in a group of apparently healthy young adult males who had normal Johnsen counts and presumably normal testicular function. It is based on the histological examination of the head of the epididymis in a group of these patients in whom part of the epididymal head had been removed during an epididymo-epididymostomy. It was hoped that this procedure would bypass the presumed obstruction without interfering with sperm maturation which possibly occurs as a result of epididymovasostomy.

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Materials and Methods

The tissue examined consisted of a wedge roughly 1.0 × 0.5 cm from the head of the epididymis. It consisted in all of the cases of some vasa efferentia and the proximal part of the ductus epididymis; in the control cases part of the rete testis was included.

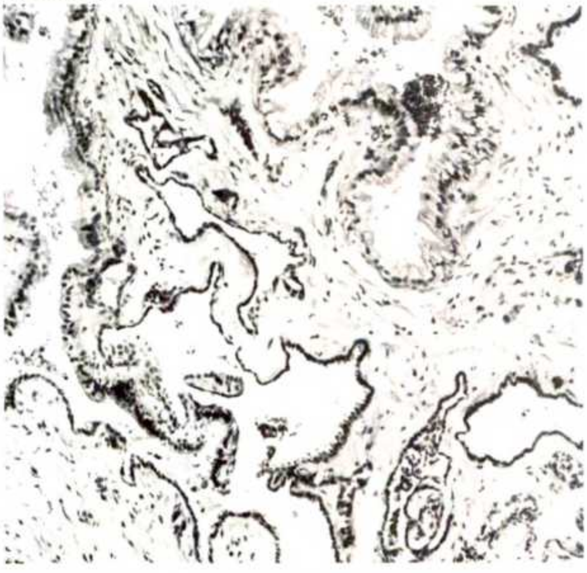

Fig. 1 Normal structure of the vasa efferentia and rete testis. The rete tubules are lined by a flattened single layer of epithelial cells. The convoluted lumen of the vasa efferentia is lined by a double layer of cells (× 105).

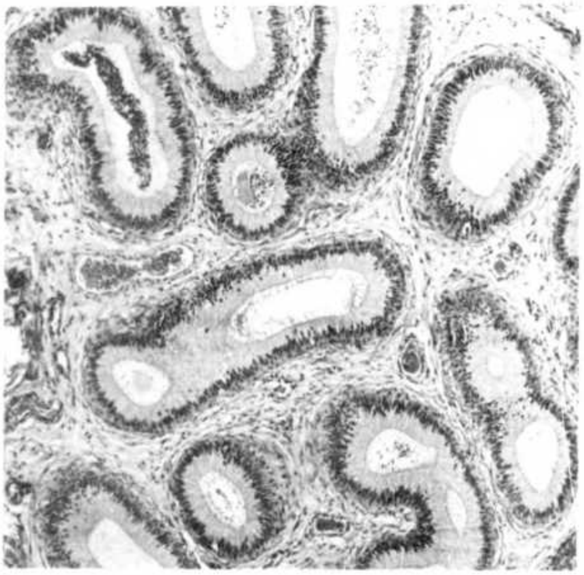

Fig. 2 Normal structure of the ductus epididymis. The tubules are lined by pseudostratified ciliated epithelial cells and spermatozoa are present within the lumen of some tubules (× 60).

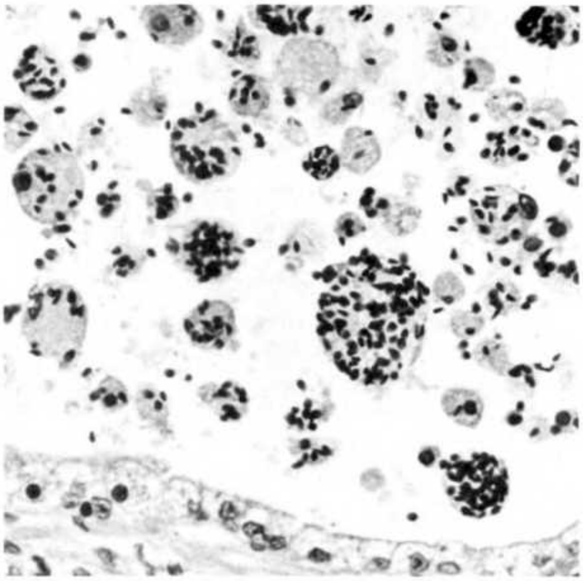

Fig. 4 Sperm clumped around mononuclear cells in a dilated vas efferens (× 375).

Forty specimens were examined.

Two specimens were from an infertile patient who was subsequently shown to have congenital absence of both vasa deferentia.

Thirty specimens were from a group of infertile patients in whom normal testicular function was associated with azoospermia and who were considered to be cases of idiopathic epididymal obstruction.

Eight post-mortem specimens from previously healthy young males who had died as a result of road traffic accidents were considered to be "normal" controls.

The specimens were embedded in paraffin and examined by semi-serial sections. The sections were routinely stained with haematoxylin and eosin and by Masson. Special staining methods were used to demonstrate lipofuchsin.

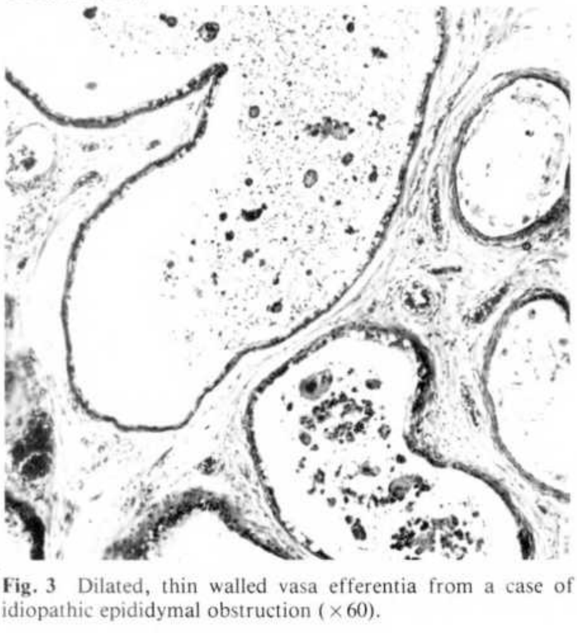

Fig. 3 Dilated, thin walled vasa efferentia from a case of idiopathic epididymal obstruction (× 60).

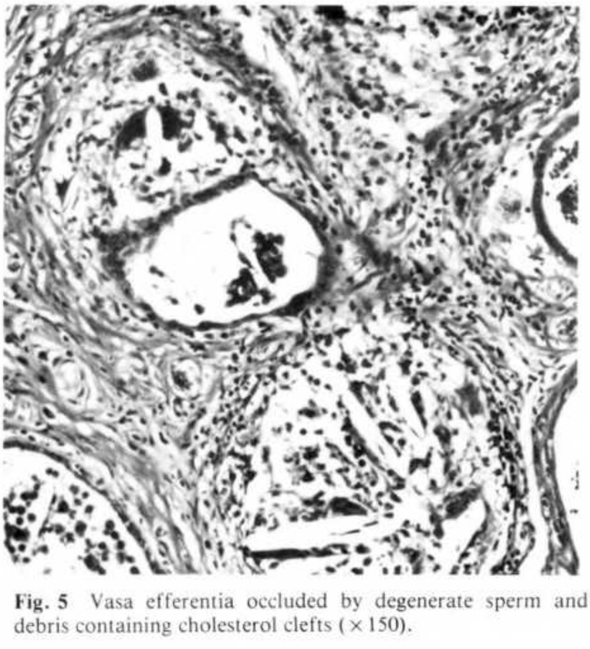

Fig. 5 Vasa efferentia occluded by degenerate sperm and debris containing cholesterol clefts (× 150).

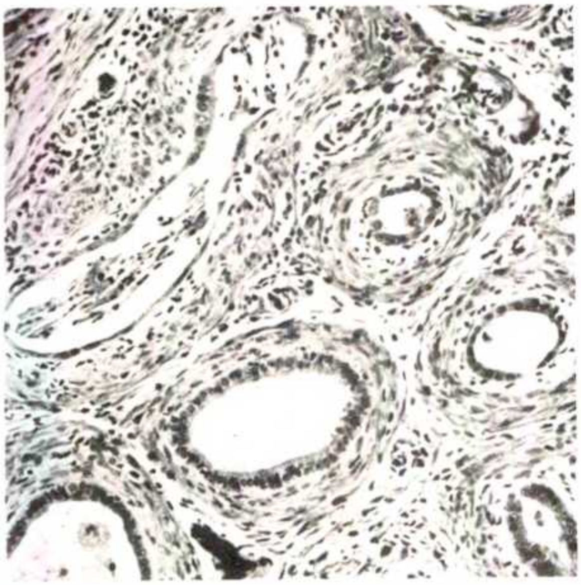

Fig. 6 Vasa efferentia showing fibrous thickening of their wall. The lumen is narrowed and lined by a single layer of non-ciliated cells (× 150).

Results

Normal Controls

The tubules of the rete were lined by a single layer of flat epithelial cells.

The vasa efferentia were surrounded by a thin layer of smooth muscle and the epithelial lining was thrown up into convoluted folds (Fig. 1). The epithelial cells were tall with a basal nucleus and abundant cytoplasm. The cytoplasm was frequently foamy and sometimes contained lipofuchsin pigment. The tubules were lined by one or 2 cells and in some parts the free border of the cell was ciliated.

The ductuli epididymis formed a system of coiled tubules which united with each other within the epididymal head. They were surrounded by a layer of smooth muscle which was thicker than that around the vasa efferentia. The lumen surface was smooth and ciliated; the cells were psuedostratified with an outer layer of flattened cuboidal cells (Fig. 2). The cytoplasm of the cells was not foamy and rarely contained lipofuchsin.

Spermatozoa were present in small numbers in the rete and vasa efferentia and in larger numbers in the ductus epididymis.

Congenital Absence of the Vas Deferens

The head of the epididymis was enlarged and congested. Histological examination showed the vasa efferentia and the ductus epididymis to be stuffed with apparently normal sperm. No tubular degeneration and no inflammation were present.

Idiopathic Epididymal Obstruction

In all of these specimens the head of the epididymis was enlarged and congested with small yellow nodules present on the surface. When the cut surface was examined these nodules were seen to consist of groups of dilated tubules from which thick creamy material oozed.

In all of the specimens of idiopathic epididymal obstruction the following histological abnormalities were present in some areas of the vasa efferentia.

Groups of tubules were grossly dilated, had lost their normal convoluted surface and were lined with a single layer of nonciliated cells which frequently contained an increased amount of lipofuchsin pigment (Fig. 3). These dilated segments corresponded to the yellow nodules noted macroscopically. They were stuffed in different areas with either (1) apparently normal sperm, (2) normal sperm and mononuclear cells, (3) clumps of sperm around mononuclear cells (Fig. 4) or (4) degenerate sperm and debris (Fig. 5). The cytoplasm of the mononuclear cells was abundant and "foamy" and it was presumed that lipid material had originally been present in the cytoplasm but had been dissolved during the processing. The cytoplasm of these cells frequently contained degenerate sperm and golden brown lipofuchsin pigment similar to that seen in the epithelial cells of the vasa efferentia. The clumping of sperm around mononuclear cells and the presence of degenerate sperm within their cytoplasm indicates a "macrophage" type role for them. Linear clefts were frequently present amongst the degenerate debris (Fig. 5) and their shape suggested that they had originally contained cholesterol crystals. The contents of these dilated tubules corresponded with the thick creamy material noted macroscopically.

Other groups of vasa efferentia showed thickening of their wall either by an infiltration with mononuclear cells similar to those seen within the lumen of some of the dilated segments or by fibrosis (Fig. 6). This was associated with narrowing and sometimes complete obliteration of the lumen. Focal interstitial collections of mononuclear cells with foamy, pigmented cytoplasm, lymphocytes

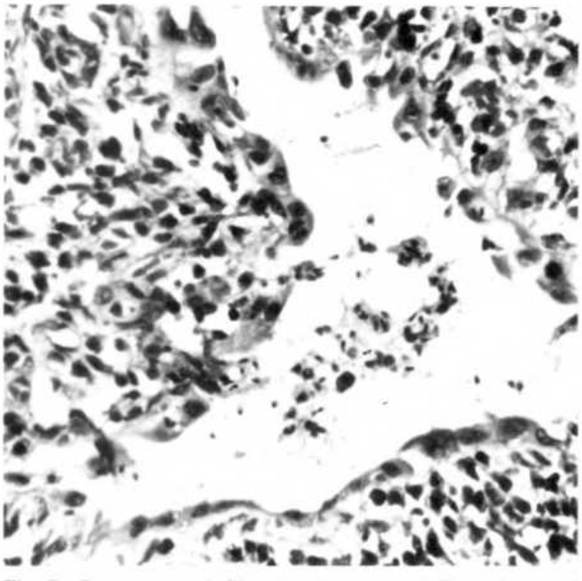

Fig. 7 Spermatozoa infiltrating through an inflamed area of the wall of a vas efferens into the interstitial tissue (× 375).

and plasma cells were present between these thickened vasa efferentia.

In all of the specimens the structure of the ductus epididymis appeared to be normal but sperm were absent from the lumen.

Additional features divided the specimens into 2 groups.

In 10 specimens (group 1) small acute inflammatory lesions were present in the wall of part of a vas efferens. Spermatozoa were seen infiltrating through the wall in these inflammatory foci and their presence in the interstitial tissue was associated with the production of a sperm granuloma (Fig. 7). This inflammatory reaction led to thickening and narrowing of the duct.

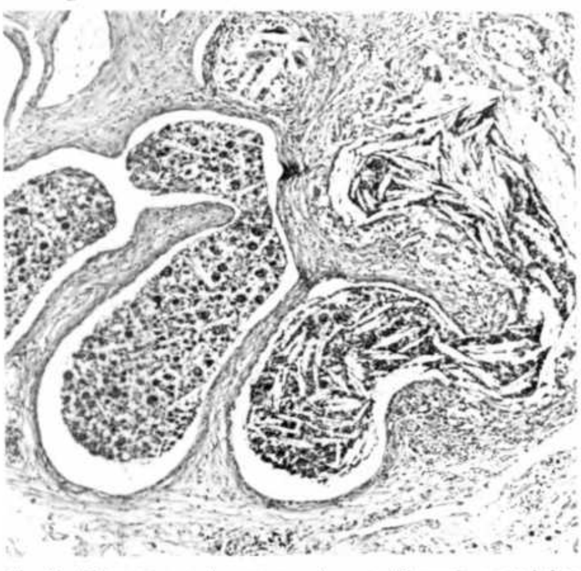

Fig. 8 Dilatation and rupture of vasa efferentia containing degenerate sperm and debris (× 60).

In 20 specimens (group 2) no acute inflammatory lesions or sperm granulomata could be found but these cases all showed extreme distension of parts of the vasa efferentia by degenerate sperm, debris and cholesterol clefts (Fig. 8). Rupture of such a thinned area was associated with the spillage of cholesterol material into the interstitial tissue and the formation of a foreign body type of granulomatous reaction. This again resulted in thickening around the duct with narrowing of the lumen and interstitial fibrosis.

Discussion

In the normal fertile human male there is an orderly passage of spermatozoa from the seminiferous tubules through the tubules of the rete testis and epididymis to the vas deferens. Spermatozoa mature during this passage and there is storage of sperm in the ductus epididymis.

The mechanism responsible for movement of spermatozoa from the testis and through the rete to the vasa efferentia and ductus epididymis is still a matter for conjecture. Sperm are not fully motile until they have passed through the epididymis. It is suggested by Hargrove *et al.* (1977) that passage from the seminiferous tubule to the rete and vasa efferentia is due to a combination of the action of contractile cells which are present within the capsule of the testis and around the epididymal tubules, and the secretion of fluid by the seminiferous tubules. They do not think that the action of cilia plays much part in sperm propulsion at this stage.

Obstruction to the distal part of the excretory passage does not appear to cause permanent damage to the testis, the epididymis or the spermatozoa. Vasectomy does not usually interfere with testicular or epididymal function although Silber (1977) has correlated the failure of vasectomy reversal with the length of time between vasectomy and reversal and has postulated that in some patients raised post-operative intra-vasal pressure can over many years lead to permanent damage to the seminiferous tubules.

In the present series, congenital absence of both vasa deferentia resulted in stuffing of the epididymal tubules with sperm but without damage to the sperm, the tubules or interstitial tissue.

McMillan (1953) considers that in cases of congenital absence of the vas deferens, tubular adjustment proceeds gradually over a period of years, providing the blood supply, lymph drainage and innervation of the testis remain intact.

The fate of the spermatozoa in cases of vasectomy or congenital absence of the vas deferens is a matter of conjecture. It has been suggested by Hulka and Davis (1972) that there may be resorption of sperm within the epididymis or that a feedback mechanism operates which decreases the rate of spermatogenesis.

Whilst simple mechanical obstruction to the distal part of the excretory passage does not cause damage to the sperm or the tubules, there is evidence that obstruction to the proximal part does do so. Hanley and Hodges (1959) described the results of microdissection of the epididymis in 2 azoospermic patients who had had normal testicular function. In both cases they demonstrated occlusion to parts of the vasa efferentia. Proximal to the block there was cystic dilatation of the lumen which was stuffed with sperm, mononuclear cells and degenerate debris. In the apparent absence of any inflammatory condition the authors presumed that the obstruction they demonstrated was congenital in origin. Their findings are similar to those reported in this paper and confirm that obstruction to the proximal part of the vasa efferentia is associated with damage proximal to the block.

Hendry *et al.* (1978) also report, in cases of obstructive azoospermia, the presence of dilated epididymal tubules. Some of these tubules had normal peritubular musculature and normal ciliated epithelium. Other tubules were lined by a flattened epithelium and contained amorphous material and prominent cholesterol clefts. Their cases included patients who had had a vasectomy and some cases of Young's syndrome. It seems probable that at least some of their cases were examples of obstruction to the proximal part of the vasa efferentia.

The specimens reported in this paper were all from patients who had been sterile for some years before investigation, so that the appearances described are presumably not those of the initial lesion. However, once the thickening and narrowing of the vasa efferentia which is present in all of these cases of idiopathic epididymal obstruction has occurred, it will present a continuing obstacle to the normal transport of sperm. In the "group 1" specimens the presence of small acute inflammatory areas in parts of the vasa efferentia suggests that in these patients the initial lesion is inflammatory. The passage of sperm through these areas into the interstitial tissue leads to the formation of small sperm granulomata. This is followed by fibrosis around the vasa efferentia with narrowing of the lumen and obstruction to the passage of the sperm. Continuing low grade infection could account for the persistence of the inflammatory foci.

In the "group 2" specimens no acute inflammatory foci or sperm granulomata are present. In this group the vasa efferentia are dilated by sperm, many of which are degenerate, and lipid rich debris. Rupture of some of these tubules with the escape of their contents into the interstitial tissue results in the formation of a foreign body granulomatous reaction around the tubule. This again leads to thickening and narrowing with obstruction to the passage of sperm.

These 2 groups may have separate aetiologies, only one of which is inflammatory, or it is possible that they represent different stages of one disease process. If the latter suggestion is correct, the initial lesion is a small focus of inflammation which leads to the development of a sperm granuloma outside the lumen. Resolution of the inflammation results in narrowing of the vasa efferentia with some obstruction. This in turn leads to dilatation of the vasa efferentia proximal to the obstruction. Increased intratubular pressure results in degeneration of sperm, damage to the epithelial lining and rupture of the wall, the formation of foreign body granulomata and further fibrosis and narrowing.

If the picture seen in the group of patients without sperm granulomata is not the late stage of an inflammatory process, it could be the result of a congenital abnormality such as described by Hanley and Hodges (1959) or of some acute obstruction in the proximal part of the head of the epididymis to the normal passage of sperm. This could be the result of damage to the tubular cells, possibly of traumatic or ischaemic origin. It is not possible to tell whether the absence of cilia in parts of the vasa efferentia plays a part in the mechanism of obstruction or whether their absence is a result of the damage to the tubular epithelium.

It is not obvious why the sperm degenerate proximal to the obstruction when it occurs in the head of the epididymis and not when the obstruction is more distal. It may be that the sperm are more immature and so more susceptible to adverse conditions. Alternatively, it may be associated with the tubular volume available to accommodate the sperm and sperm fluid—the limited volume available when the obstruction is in the head of the epididymis causing greater pressure in the proximal tubules.

The presence of spermatozoa within connective tissue is known to excite an inflammatory reaction. The first case of an epididymal sperm granuloma was described in 1931 and there are now over 100 recorded cases. The largest series is that of Glassy and Mostofi (1956) who described 61 cases. In some cases the epididymal sperm granulomata were discovered at routine post mortem examination but they were usually found during investigation of a painless epididymal swelling. The histological appearances were well described by Glassy and Mostofi and they are similar to but considerably more extensive than those described in this paper.

There is debate as to how the sperm enter the interstitial tissue. It is suggested that an inflammatory or traumatic epididymitis allows the sperm to enter the tubular epithelial cell and pass through to the interstitial tissue. Approximately one-third of the cases described by Glassy and Mostofi gave a history of previous epididymitis. Although no history of epididymitis is present in any of the cases described in this paper, there is histological evidence of foci of acute inflammation in 10 cases. A history of trauma was present in 9 of the cases described by Glassy and Mostofi (1956) and in 4 of the 5 cases described by Rovinescu and Reid (1966).

McMillan (1953) showed that the initial segment of the ductus epididymis in rats is very susceptible to ischaemia. The changes which result lead to temporary obstruction of the excretory pathway. Unless this is speedily resolved the vasa efferentia cannot withstand the pressure of the accumulated sperm cells and fluid. Disintegration of the epithelial lining is followed by fibrous replacement of the efferent pathway. He suggests that interference with the epididymal blood supply during surgical procedures in the inguinal region, or even prolonged vasoconstriction, may lead to ischaemic damage of the epididymal head and subsequent infertility.

Povysil (1976) produced epididymal sperm granulomata in rats by experimental ischaemia and suggested that ischaemia may also play a part in damaging the tubules in the human epididymis with the consequent passage of spermatozoa through the wall.

This study describes the histological findings in a group of patients in whom normal testicular function was associated with azoospermia. In all of the cases severe narrowing and fibrosis of segments of the vasa efferentia, with replacement of the normal epithelium by a thin layer of cells, presented an obstruction to the passage of sperm. Increased pressure behind the obstruction was associated with further tubular damage.

The original causes of the condition are still obscure. It is very likely that in some cases at least a low grade chronic inflammatory epididymitis was the cause. Other cases may have an initial ischaemic origin as a result of minor trauma or there may be a congenital abnormality within the vasa efferentia.

Acknowledgement

I wish to thank Mr J. G. Gow for permission to publish the histological details of his series of patients with idiopathic epididymal obstruction in whom epididymo-epididymostomies had been carried out in an attempt to restore fertility.

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Evaluation of Computed Tomography in the Management of Testicular Teratoma

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Summary—An analysis has been made of data obtained by computed tomography (CT) scanning in 100 patients with testicular teratoma. The results have been compared with information obtained by conventional staging procedures and changes in patient management occurring as a direct result of CT have been noted. Although these tumours are rare, their pattern of metastasis to the retroperitoneum, mediastinum, lungs and liver is consistent. Thus the value of CT scanning can be tested in all of these sites in each patient and the indications for scanning clearly defined.

It is widely assumed that the use of CT scanning in patients with malignant disease will give more information than that obtained by conventional investigations, and that this increased information will lead to improved treatment and possibly survival. However, few critical analyses of the influence of CT on patient management are yet available. In order to use limited facilities most effectively and to avoid unnecessary investigation for the patient, indications for scanning need to be clearly defined.

Patients and Methods

One hundred consecutive patients seen at The Royal Marsden Hospital, Sutton, were studied. Of these, 54 were previously untreated, new patients (Group A) and 46 were patients who had previously been treated before the first CT scan was carried out (Group B). All new patients underwent staging investigations as shown in Table 1. All patients were investigated in a similar manner if clinically indicated but not all tests were performed on each occasion.

The staging classification used in the Testicular Unit and treatment policies according to stage are shown in Table 2. The rationale of these policies has been discussed in detail elsewhere (Peckham *et al.*, 1979).

Two hundred and five CT scans were performed at intervals of 2 to 6 months in this group of 100 patients. The CT scans were carried out using an EMI Whole Body Scanner (CT 5005), which has a scan time of 20 s and a slice thickness of 13 mm. CT sections were taken through the chest at 1 cm intervals and through the abdomen at 2 cm intervals down to the lower border of the fifth lumbar vertebra. All patients were given an oral contrast medium (sodium/meglumine diatrizoate—Gastrografin 5% solution 300 ml) 30 min before scanning the abdomen to opacify the small bowel, because this has a density similar to that of other soft tissue and may therefore simulate tumour. An anticholinergic agent (hyoscin-N-butyl-bromide (Buscopan) 20 mg intramuscular injection) was also given 5 min before the abdominal scan to reduce streak artefacts from gas in moving bowel. Intravenous contrast medium was not routinely given but reserved for examination of the liver if metastases were suspected on the initial series of

Table 1 Testicular Teratoma Routine Investigations

Radiology/imaging	*Other*
PA chest film	Review histology
Whole lung tomography	Full blood count, urea, electrolytes
Lymphography	Liver function tests + αG-T
Intravenous urography	EDTA clearance test
Liver and spleen isotope scan	Serum markers (AFP and HCG)
Liver and abdominal ultrasound	(Lung function tests)
CT scan of thorax and abdomen	(Semen analysis)

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Table 2

Stage		*Definition*	*Treatment policy*
I		No detectable residual disease after orchiectomy	R/T—para-aortic nodes and ipsilateral pelvic nodes ± scrotum
II	a	Abdominal nodes<2 cm	R/T as for Stage 1
	b	Abdominal nodes<5 cm	
	c	Abdominal nodes>5 cm No disease elsewhere	Chemotherapy → R/T → surgery
III*		Supradiaphragmatic and abdominal disease	
	M+	Mediastinal involvement	Chemotherapy → R/T
	N+	Neck node involvement	
IV*	L_1	≤ 3 pulmonary metastases	
	L_2	Multiple small metastases	
	L_3	Multiple metastases>2 cm diameter	Chemotherapy ± R/T
	H+	Liver involvement	

* Abdominal status III and IV defined as for Stage II

Table 3 Comparison of CT with Lymphography in Testicular Teratomas in 52 Patients (Group A)

Lymphogram	*No. patients*	*CT findings*	
		Negative	*Positive*
Negative	18	16	2*
Positive	31	1	30*
Equivocal	3	3	—
Total	52	20	32

* Additional information obtained with CT.

scans, or to help to differentiate vascular structures from suspected lymphadenopathy.

Results

The abnormal CT appearances in testicular teratomas have been described elsewhere (Husband *et al.*, 1979).

Our CT findings have been analysed in 2 ways:

1. Direct comparison of CT with conventional radiological techniques and ultrasound.
2. Analysis of changes in stage and treatment as a direct result of CT scanning.

Direct Comparative Analyses

Lymphography Table 3 shows the results of a comparison between lymphography and CT findings in 52 out of 54 new patients. The investigations were carried out within 2 weeks of each other. The results show that overall there was good concordance between the 2 methods. There were 2 false negative examinations with lymphography and 1 false negative examination with CT. Subsequent follow-up in the 3 patients with equivocal lymphograms proved that the negative CT examinations were correct. Sufficient time has now elapsed for follow-up scans to be performed in 23 of the 54 new patients. The results are shown in Table 4 and indicate that CT is more effective in detecting persistent disease than the lymphogram follow-up radiograph, since 9 out of 18 patients had positive CT scans after the lymphogram appearances had returned to normal.

In 41 patients in Group B, the initial CT scan findings were compared with a follow-up lympho-

Table 4 Comparison of Lymphogram Follow-up Film With CT Findings in Testicular Teratomas in 23 out of 52 New Patients (Group A)

Follow-up scan		*LG+*	*CT+*	*LG−*	*CT−*	*LG−*	*CT+*
No of patients	*No. of scans*	*No. of patients*	*No. of scans*	*No. of patients*	*No. of scans*	*No. of patients*	*No. of scans*
18	(27)	6	(11)	3	(3)	9	(13)
5	(13)	—	—	5	(13)	—	—
23	(40)	6	(11)	8	(16)	9	(13)

Table 5 Comparison of Lymphogram Follow-up Film With CT Findings in Testicular Teratomas in 41 Patients Previously Treated (Initial CT Scan Compared With Follow-up Abdominal Radiograph—Group B)

Initial lymphogram		*Follow-up*			
		LG+ CT+	*LG+ CT−*	*LG− CT+*	*LG− CT−*
Positive	15	5	1	9	—
Negative	26	—	—	—	26

Table 6 Comparison WLT and CT in Testicular Teratomas in 96 Patients (Groups A and B)

Whole lung tomograms		*CT findings*	
	No. of patients	*Positive*	*Negative*
Positive	31	31	—
Negative	65	5	60
Total	96	36	60

gram radiograph taken at the same time as the scan (Table 5). In 5 of those in whom the original lymphogram had been positive, both the CT scan and the follow-up abdominal radiograph showed no evidence of disease, whereas in 9 patients CT alone was positive.

Immediately after lymphography CT and lymphography are equally accurate; however, during follow-up, CT becomes progressively more important in the detection of persisting disease because the lymphographic contrast is gradually resorbed from the involved nodes.

Whole Lung Tomography Table 6 shows that there was only a small yield of positive CT scans in the lung when the whole lung tomograms were negative. However, CT often gave additional information: increased number of metastases, better definition of size or detection of metastases in sites such as the hilar region, which are not easily visualised on conventional whole lung tomograms.

This extra information was of importance in determining treatment policy. Sequential studies in 35 patients showed that scans remained positive longer than whole lung tomograms and, in patients with developing disease, showed changes earlier.

Assessment of Mediastinal Involvement Twelve patients out of 96 (Groups A and B) had mediastinal involvement which was demonstrated by CT scanning alone in 7 and by conventional radiography and CT in the rest.

Ultrasound A comparison of results between CT scanning and ultrasound in the detection of abdominal lymphadenopathy and liver involvement is shown in Tables 7 and 8. Since only 8 patients were shown to have liver metastases, it is difficult to draw conclusions regarding the relative accuracy of ultrasound and CT. Involvement was detected by CT scanning in 6 cases and by ultrasound in 4. Because of the difficulty of accurate determination of disease in this site we would recommend the use of all available methods for accurate assessment. Liver involvement was confirmed by laparotomy, biopsy, or post mortem examination in all patients except in 1 patient with a positive ultrasound only, who is alive with no evidence of disease 15 months later.

Analysis of Changes in Stage and Treatment as a Direct Result of CT Scanning

Table 9 shows that CT led to a change in stage in 7 patients (12%) compared with conventional staging. Treatment policy was altered in 31 out of 100 patients as shown in Table 10. In 10 patients where relapse was suspected clinically but CT scanning was negative, no treatment was given.

Table 7 Correlation Between CT and Ultrasound in Testicular Teratomas; Retroperitoneum—89 Patients

Final status		*CT findings*				*Ultrasound*				
		Correct	*False +*	*False −*	*TF**	*Correct*	*False +*	*False −*	*Eq*	*TF**
Positive	46	43	—	2	1	23	—	15	1	7
Negative	43	43	—	—	—	35	3	—	—	5
Total	89	86	0	2	1	58	3	15	1	12

* TF = technical failure.

Table 8 Correlation Between CT and Ultrasound in Testicular Teratomas; Liver—89 Patients

Final status		*CT findings*				*Ultrasound*			
		Correct	*False +*	*False −*	*Equiv.*	*Correct*	*False +*	*False −*	*TF*
Positive	8	6	—	2	—	4	—	3	1
Negative	81	80	—	—	1	78	1	—	2
Total	89	86	—	2	1	82	1	3	3

* TF = technical failure.

None of these patients relapsed subsequently with a minimum follow-up time of 6 months. In a further 6 patients who eventually proved to have recurrent disease, CT scanning was positive in 5 and negative in 1. CT planning in 6 patients led to changes being made to the conventional treatment plans in 4. Detailed results of CT in radiotherapy planning in a larger group of patients have previously been described (Hobday *et al.*, 1979).

Discussion

Although testicular teratoma is a rare tumour, it is of considerable importance because effective treatment is now available (Samuels *et al.*, 1976; Einhorn and Donohue, 1977; Peckham *et al.*, 1979). Accurate staging is therefore essential in order to identify those patients who require chemotherapy and to avoid unnecessary treatment in those with early disease. The results of our study have shown that CT is a more sensitive method of demonstrating pulmonary, mediastinal and persisting abdominal lymphadenopathy than the techniques previously available and, as a result of this increased diagnostic accuracy, CT scanning has made a significant contribution to staging and management in a high proportion of patients. Long-term follow-up is necessary to assess the validity of these results but our initial experience suggests that the number of false positive examinations is small; false negative examinations must be expected since microscopic disease cannot be detected.

Table 9 Comparison of Conventional Staging† and CT Staging in 54 Patients (Group A)

Conventional stage	*No. of patients*	*CT stage*			
		I	*II*	*III*	*IV*
I	13	11			2
II	16		14		2
III	5			3	2
IV	20				20*
Total	54	11	14	3	26

* One patient Stage IV changed from L_1-L_2 with CT.

† Conventional staging included whole lung tomography, lymphography, intravenous urography, ultrasound and isotope imaging

According to our results, assessment of this particular group of patients with CT scanning alone would be entirely satisfactory. However, the high cost, limited availability and low daily patient through-put precludes its use in our unit in all patients. It has therefore been necessary to define a group of patients for whom CT scanning is essential and use conventional methods where these are appropriate. The following are therefore our indications for CT scanning at present.

All New Patients

(1) Patients with large volume lung metastases do not need a lung scan as their lesions are easily shown on chest X-ray, but the liver is scanned to exclude disease there, since this has been shown in our series to have prognostic significance.

(2) If any change in treatment is proposed and adequate assessment of the disease cannot be

Table 10 Influence of CT on Treatment Policies (100 Patients)

Treatment	*Change*	*No. of patients*
Chemotherapy	Introduced	9
	Continued	5
	Stopped	1
	Drugs changed	2
Surgery	Indicated by CT	1
	Contraindicated	2
Radiotherapy	Introduced	1
No treatment		10
Total change		31 (31%)

made by conventional investigations, CT scans should be repeated. For example, patients with evidence of enlarging lung metastases on a chest X-ray will not require repeat scanning before chemotherapy is changed.

(3) If local treatment such as radiotherapy or surgery is proposed, patients should be rescanned before starting this treatment to exclude metastases outside the local treatment area.

(4) In patients who have been in clinical remission but in whom relapse is suspected, either clinically or on the basis of marker elevation, scanning is again indicated.

There is clinical evidence indicating that patients with small volume metastases show a better response to radiotherapy (Tyrrell and Peckham, 1976) and chemotherapy (Samuels *et al.*, 1976) than those with bulky tumour deposits. From these observations we would expect that the earlier diagnosis of metastases by tumour markers and/or physical detection methods such as CT will lead to improved prognosis.

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Chemotherapy in Non-seminomatous Testicular Tumours Stage I

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Summary—Chemotherapy improves the survival rate of patients with disseminated teratoid testicular tumours, but patients without evidence of metastatic spread are not usually given further treatment after retroperitoneal lymphadenectomy because of the high toxicity of most drugs; 10 to 20% of these patients die later with widespread disease.

In an earlier series of 24 patients from our hospital the survival rate in stage I disease was below 70%. Since 1973, when we began to use adjuvant chemotherapy in this group, there have been no relapses.

Radical retroperitoneal lymphadenectomy has improved the outcome for patients with non-seminomatous germ cell tumours of the testis (Staubitz *et al.*, 1969; Skinner and Leadbetter, 1971; Skinner, 1976) but even greater importance can be ascribed to chemotherapy. Using cytotoxic drugs it seems possible to cure these patients even when the disease is widespread (Cvitkovic *et al.*, 1976; Einhorn and Donohue, 1977a). Since triple-drug therapy was introduced by Li *et al.* (1960), development has been rapid. With a combination of vinblastine (Velban) and bleomycin (Samuels *et al.*, 1975), a remission rate of 39% was reported for advanced disease, but some patients relapsed later. When cis-platinum was added to the combination, however, the survival rate for stage III disease (Fraley *et al.*, 1979) seemed to be over 50% (Einhorn and Donohue, 1977b).

Although much interest has been paid to cases with advanced stages of the disease, there have been few reports on the outcome for patients without evidence of metastases. In an earlier series of patients treated at our clinic between 1958 and 1967, 24 were found to be free of metastases when investigated by chest X-ray, cavography, intravenous urography, lymphangiography and retroperitoneal lymph node dissection. After orchiectomy and lymphadenectomy, no further treatment was given. However, 8 patients developed tumour recurrence within 2 years (Fig.) and they all died despite further treatment (chemotherapy, irradiation). The incidence of relapse was not related to the degree of differentiation of the primary tumour (Table 1). Encouraged by the promising results using mithramycin in the treatment of advanced non-seminomatous germ cell tumours of the testis (Kennedy, 1970a; Ekman and Almgård, 1975) we decided to treat this group of patients by chemotherapy also, although no sign of remaining disease could be detected. This study reports our experience with adjuvant chemotherapy in patients with stage I non-seminomatous germ cell tumours of the testis.

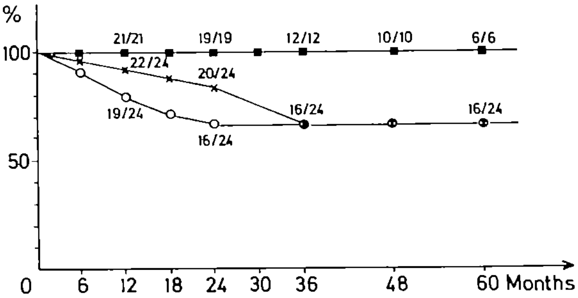

Fig. —o—o— Disease-free survival of 24 patients with teratoid testicular tumours stage I not given adjuvant chemotherapy after lymphadenectomy (collected at the Karolinska Hospital between 1958 and 1967). —x—x— Survivors among these 24 patients with teratoid testicular tumours stage I not given chemotherapy until relapse occurred. —■—■— Survival of patients with teratoid testicular tumours stage I given adjuvant chemotherapy (1973-1979).

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Table 1 Classification* of Patients with Non-Seminomatous Germ Cell Tumours of the Testis Stage I and Relation to Survival

Type of tumour	*1958-1967*	
	Total number	*Alive*†
Teratoma, mature	3	2
Teratoma immature	3	3
Embryonal carcinoma with teratoma (teratocarcinoma)	6	4
Embryonal carcinoma	12	7
Total	24	16

* According to WHO (Bar and Hedinger, 1976).
† Time interval 12 to 21 years.

Materials and Methods

Since 1973, 28 patients with stage I disease have entered the trial. Their mean age was 32 years (range 18-60) and they were all subjected to radical lymphadenectomy after orchiectomy. In 3 cases the dissection was bilateral; in the others it was restricted to the tumour side. The degree of differentiation of the tumours is given in Table 2. In no case was metastatic spread demonstrated by histological examination of the removed specimens, and serum markers AFP and HCG were normal in all cases. All patients received mithramycin 25 μg/kg body weight, suspended in a 500 ml saline solution and administered as a slow intravenous drip over 5 to 7 h. The infusion was given daily on 10 consecutive days and was repeated every 5 weeks to a total of 6 to 9 courses during one year. Because of hepatic toxicity, 3 patients were given a combination of vinblastine, actinomycin D and methotrexate after a few mithramycin courses.

The following laboratory investigations were performed on alternate days during treatment: one-stage prothrombin time (Normotest®), platelet count, active prothrombin time, serum creatinine, bilirubin and liver enzymes. No new courses of chemotherapy were started until all laboratory data had returned to normal. Before each course the serum markers AFP and HCG were checked. Chest X-ray was performed every 3 months. Six months after completion of therapy a seminal analysis was carried out.

Table 2 Classification* of Patients with Non-seminomatous Germ Cell Tumours of the Testis Stage I Treated with Mithramycin (1973-1979)

Type of tumour	*Number*
Teratoma, mature	1
Teratoma immature	4
Embryonal carcinoma with teratoma (teratocarcinoma)	6
Embryonal carcinoma	17
Total	28

* According to WHO (Bar and Hedinger, 1976)

Results

The side effects of mithramycin are well known (Ream *et al.*, 1968; Monto *et al.*, 1969; Kennedy, 1970b; Ekman and Almgård, 1975). Most patients experienced marked hepatic toxicity with nausea and vomiting. The drug has also been reported to cause transitory myocardial ischaemia fever and paresthesia renal failure, psychogenic disturbances and a bleeding diathesis (Brown and Kennedy, 1965). A tendency to bleeding was rarely encountered in our series; when it did occur it was due to an increase in fibrinolytic activity and only a few courses had to be deferred because of this. Three patients refused further therapy after ½, 1 and 3 courses because of subjective discomfort. The patient who stopped therapy after 3 courses is alive after 1½ years, whereas the other 2 died with widespread disease after 1½ and 2½ years.

Of the remaining 25 patients all are alive and without evidence of disease; 19 have been followed for more than 2 years and 6 for more than 5 years (Fig.). Thus in no patient has the tumour progressed during or after completion of chemotherapy. Three patients experienced retrograde ejaculation, 2 having undergone bilateral lymphadenectomy. Spermiograms were checked after completing chemotherapy in 8 cases; 7 were normal and one was azoospermic. The latter patient was 44 years old and had not fathered any children. His remaining testicle was atrophic. Unfortunately, in no case were sperm tests made before the gland dissection.

Discussion

The prognosis of patients with advanced non-seminomatous germ cell tumours of the testis has dramatically improved thanks to the introduction of new cytotoxic agents. However, the toxicity of these drugs, with a reported mortality of roughly 8 to 10% (Einhorn and Donohue, 1977b; Stoter *et al.*, 1979), has restricted their use to advanced stages of the disease. The follow-up period with these new drugs is still too short to calculate accurate survival figures. Less advanced cases, *i.e.* with no sign of metastases or with minimal retroperitoneal involvement as disclosed by radical bilateral lymph node dissection, have usually been left untreated until recurrence is noted. However, a mortality rate of 10 to 25% has been reported in stage I disease (Maier *et al.*, 1969; Skinner, 1976). That the figure in our "control group" from 1958 to 1967 is higher (>30%) may be ascribed to the fact that most patients were subjected to unilateral gland dissection and some may therefore have been wrongly classified. Our surgical technique has not changed, however, and the 2 series may well be compared. It seems as if patients with micrometastases may be cured by the present treatment.

Mithramycin has proved its value in the treatment of teratoid testicular tumours. Apart from new drug combinations, such as cis-platinum, vinblastine and bleomycin, it has had the highest reported incidence of complete remissions (Smithers, 1972). However, it has more or less fallen into oblivion, partly because of the interest in new drugs but also because of the reported high risk of a bleeding diathesis (Brown and Kennedy, 1965). In our hands, bleeding has been a minor problem and only one patient out of 95 has died from haemorrhage. This was at an early stage of the trial, when our experience was limited. At operation the patient was found to have inoperable bulky retroperitoneal metastases and died after completing 2 courses of mithramycin; at autopsy the metastases were converted to fibrotic tissue with no teratoid components.

Monto *et al.* (1969) reported that coagulation factors II, V, VII and X were depressed by mithramycin therapy. We have found that treatment with calcium and epsilon-amino-caproic acid is of value and can be recommended when laboratory data indicate an increased risk of bleeding. An increase in liver enzymes is by far the most common complication of mithramycin therapy. However, this effect is rapidly reversible and the change of therapy undertaken in 3 cases (see above) was not necessary.

An adequate radical bilateral retroperitoneal lymph node dissection is generally complicated by retrograde ejaculation and azoospermia due to injury to the sympathetic nerve system (Kedia *et al.*, 1977). In the present series, only 3/26 patients (2 of whom had undergone bilateral dissection) experienced retrograde ejaculation. Our results indicate that when the radical dissection is limited to one side, sexual function can be expected to remain intact and if patients in stage I are given adjuvant chemotherapy, the survival rate seems to approach 100%. Centres earlier devoted to bilateral high retroperitoneal lymphadenectomy now question the adequacy of this approach in low-stage disease (Donohue *et al.*, 1978). In Donohue's series of 30 stage A patients, all were subjected to extensive suprahilar bilateral dissection; 3 relapsed but remain alive following aggressive combination chemotherapy. All patients had ejaculatory impotence. The Royal Marsden Hospital regimen, based on orchiectomy and radiotherapy alone in low-stage non-seminomatous germ cell tumours of the testicle, obviously has no adverse effects as far as future fertility is concerned (Peckham, 1979). Although a relapse rate of 20% was reported, half of these relapses were cured by aggressive chemotherapy. Most relapses occurred in the supradiaphragmatic region outside the irradiated field but well accessible to adjuvant chemotherapy. The disadvantages include a high risk of erroneous staging when lymphadenectomy is not performed (Clements *et al.*, 1979), reduced tolerance to possible future chemotherapy and the risk of radiotherapy-induced malignancy (Lynch and Herr, 1980). In our present treatment of non-seminomatous germ cell tumours of the testis, therefore, bilateral retroperitoneal exploration is performed and, if no suspect glands are found, the dissection is limited to the tumour side.

Since dissection is restricted to one side in order to preserve fertility, it is important to ensure that chemotherapy does not irreversibly damage the remaining testicle. The present investigation indicates that the sperm count is slightly depressed during mithramycin therapy but returns to normal after completion of treatment. A few patients in the present series and several patients with more advanced disease have fathered normal children after chemotherapy. The wife of a patient in this series became pregnant between the fourth and fifth course of treatment. Abortion was recommended, since we have no proof that the therapy is not temporarily teratogenic.

Conclusions

When using mithramycin as adjuvant chemotherapy in patients with stage I non-seminomatous germ cell tumours of the testis, the survival rate seems to approach 100%. These findings are based on a series of patients who, with a few exceptions, were subjected to unilateral gland dissection with preservation of normal sexual function. We therefore perform a bilateral retroperitoneal exploration but restrict the dissection to the tumour side if no metastases are found. All patients are then given adjuvant chemotherapy (mithramycin) for at least 6 months.

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Case Reports

Absence of Both Seminal Vesicles Associated with Hypospermatogenesis

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Case Report

A 26-year-old man presented with sterility and decrease in the volume of ejaculate. His external genitalia and chromosomes were normal. The volume of one ejaculate was no more than 1.5 ml and no spermatozoa were found. Urine analysis, excretion urography, urethrocystography and endoscopic examination were normal. A vesiculogram showed both ampullae of the vasa deferentia to be deviated to the left and neither seminal vesicle was visualised (Fig. 1). The absence of seminal vesicles was confirmed at operation. Testicular biopsy showed hypospermatogenesis (Fig. 2).

Comment

Anomalies of the seminal vesicle, which derives from the mesonephric duct, are often associated with other anomalies of the genitourinary tract (Fuselier and Peters, 1976; Campbell and Harrison, 1978). However, there are few reports of absent seminal vesicles (Sargent *et al.*, 1970).

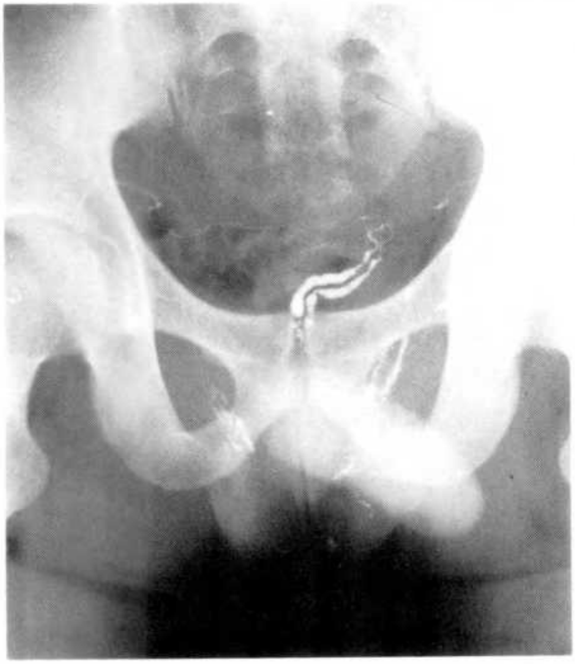

Fig. 1 Bilateral vesiculogram.

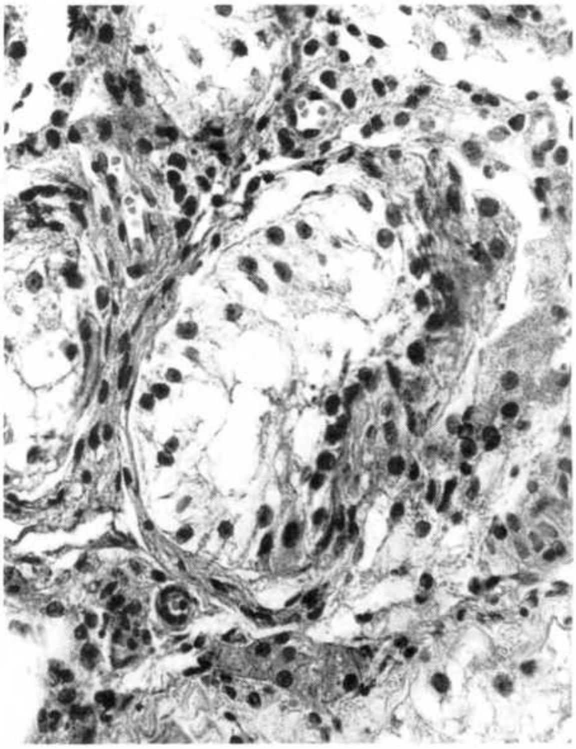

Fig. 2 Testicular biopsy. Stained (H and E ×40).

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Carcinoma of the Kidney as a Cause of Spontaneous Peripelvic Extravasation

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Renal cell carcinoma of the kidney may bleed so severely that clots form and cause colic as they pass down the ureter. This patient presented with clot colic and the initial intravenous urogram demonstrated urinary extravasation. The IVU made after the acute symptoms had disappeared was normal.

Case Report

A 53-year-old male presented with right ureteric colic soon followed by the passage of clots. An emergency IVU (Fig.) demonstrated a mild right hydronephrosis with extravasation of contrast material around the pelvis. The ureter was dilated to the bladder. Two days later, when all symptoms had disappeared, another IVU was normal. Renal arteriography demonstrated the vascular pattern of a tumour in the lower pole of the right kidney. A radical nephrectomy was carried out and histological examination revealed an adenocarcinoma.

Comment

Acute or chronic ureteric obstruction, trauma, surgery or external pressure can cause extravasation of urine from the renal pelvis or calices. The rupture occurs usually in the fornix of a calix, sometimes in the pelvis or the ureter, and the kidney continues to function. Kettlewell (1973) showed that rupture can result whenever pressure in the pelvis exceeds 50 mmHg. Once the fornix ruptures, urine extravasates around the pelvis and is reabsorbed by the lymph vessels, by the veins, by the perivascular spaces or by the retroperitoneal tissues.

Acute ureteric obstruction is most commonly caused by a stone and emergency intravenous urography often demonstrates extravasation, which disappears in about 24 h. Sometimes acute obstruction results in a urinoma (Ramsey *et al.*, 1973).

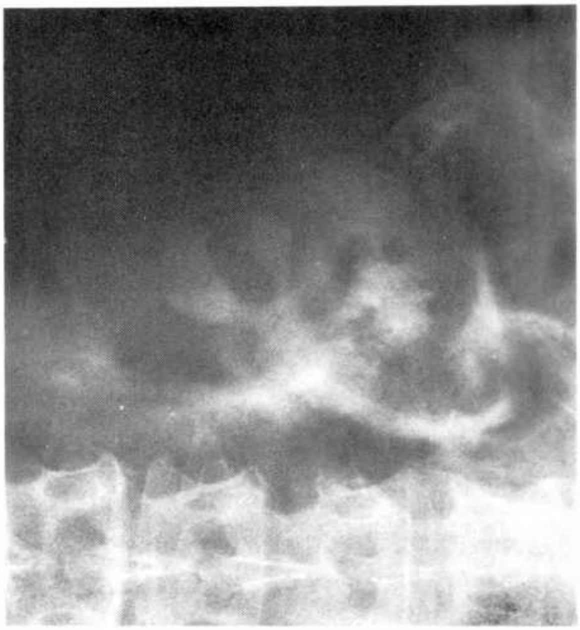

Fig. IVU demonstrates mild right hydronephrosis with extravasation of contrast material around the pelvis.

In this case peripelvic extravasation resulted from clot obstruction of the ureter and when the obstruction was relieved, the "leak" sealed and the urine was reabsorbed.

Spontaneous peripelvic extravasation combined with ureteric colic is usually caused by ureteric stones, but when clot formation is present a renal tumour has to be considered.

References

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0007-1331/81/00460190$01.00

Appendicovesicocolic Fistula

A. R. E. BLACKLOCK, *Department of Urology, Walsgrave Hospital, Clifford Bridge Road, Coventry*

Vesicointestinal fistulae are not uncommon and are usually due to communication between the bladder and large bowel. Much less common are fistulae involving the appendix. A case is described of an appendicovesicocolic fistula.

Case Report

A 45-year-old man presented with a 6-month history of diarrhoea, recurrent urinary tract infections, pneumaturia and the passage of faecal material in his urine. He had had no previous symptoms of "appendicitis".

Investigations showed neutrophil leucocytosis and an *Escherichia coli* urinary tract infection. Excretion urography was normal. Barium enema showed early diverticular disease in the sigmoid colon without obstruction or leak. Cystoscopy revealed an inflamed bladder with a polypoid mass on the posterior wall, biopsies of which showed chronic inflammation of the bladder wall and normal colonic mucosa. At laparotomy the necrotic tip of the appendix was found lying in an abscess cavity which communicated with the sigmoid colon and bladder (Fig.). Retrograde appendicectomy and limited sigmoid colectomy were performed, excising the fistula. Examination of the appendix and colon showed marked inflammation around the fistula but no evidence of malignancy or granuloma formation.

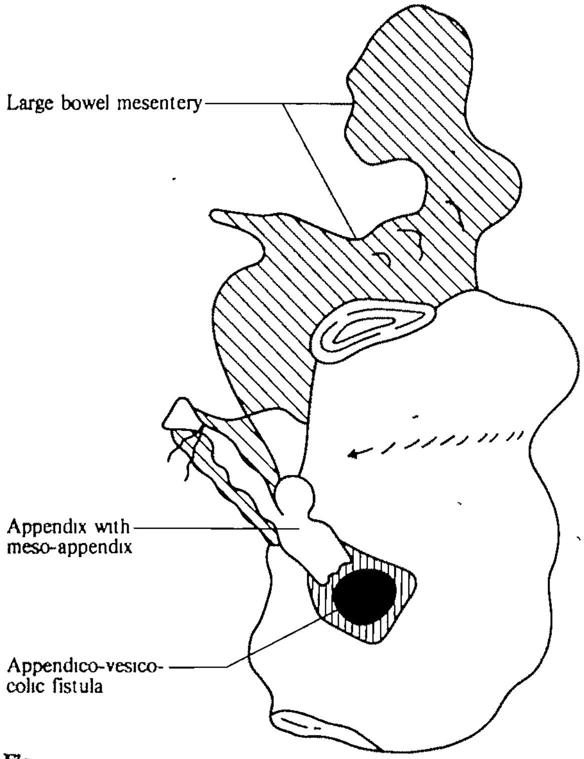

Fig.

Comment

The commonest cause of vesicointestinal fistulae are diseases of the large bowel, *i.e.* diverticulitis, carcinoma and (more rarely) Crohn's disease or ulcerative colitis. It is very rare for the primary condition to be in the bladder.

Cases of appendicovesical fistula have been described as secondary to appendicitis (Parton, 1958) or tumour of the appendix (Di Paola and Tockwell, 1976), but only one previous case of appendicovesicocolic fistula has been found in the literature (Marshall *et al.*, 1975). In this case it appears that an abscess developed in a pelvic appendix lying between the sigmoid colon and bladder base and was responsible for the development of the appendicovesicocolic fistula.

Acknowledgement

I wish to thank Mr P. Dawson-Edwards for his advice and permission to report this case.

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A Case of Heterotrophic Ossification of Bladder

D. JAGADISAN, G. RAJENDIRAN, D. PREMKUMAR and M. SIVAJI, *Department of Urology, Stanley Medical College, Madras, India*

A case of recurrent vesical stone with heterotrophic ossification of the bladder in a female patient is presented.

Case Report

A female aged 25 years was admitted to the Government Stanley Hospital, Madras, complaining of painful micturition and suprapubic pain. She had undergone transvaginal cystolithotomy in a maternity hospital 8 months previously for vesical stone. There was no evidence of vesicovaginal fistula. A plain X-ray revealed a vesical stone and another radio-opaque shadow overlying the sacrum. An intravenous nephrogram and biochemical investigations were normal. Under general anaesthesia the bladder was opened and a large stone removed (Fig.). The bladder mucosa near the fundus of the bladder was indurated and a piece of bone embedded in the vesical mucosa was removed. The histopathological investigation of the bladder mucosa showed inflammatory reaction. Histology confirmed the bone.

Comment

That vesical mucosa can induce new bone formation is well known. In this case ossification of the bladder mucosa may have been due to the recurrent vesical stone. Heterotrophic ossification occurs in fibrous connective tissue and in structures that are in a state of functional decay. Metaplasia of non-osseous into osseous tissue occurs without the preliminary formation of osteoid. The new bone develops as membranous bone which is gradually replaced by lamellar bone, and finally ectopic bone is indistinguishable from the normal bone. Primitive cells can assume an osteoblastic function in the presence of increased vascularity and calcium and experiments have shown that the transplanting of vesical mucosa into bone defects induces first cartilagenous tissue and later bone.

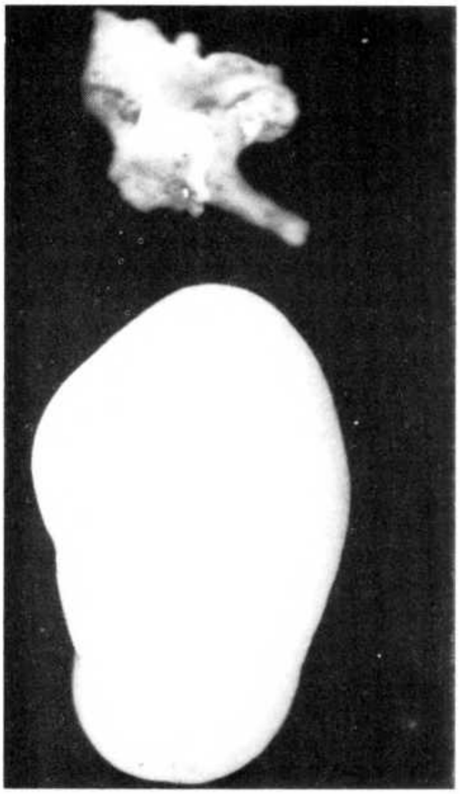

Fig. The vesical stone and the bone.

Requests for reprints to: D. Jagadisan, 26/3, Sait Colony, 2nd Street, Madras-8, India.

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Aspergillus flavus in Prostatic Fluid

S I KARAYANNOPOULOS and A STYLIANEA, *Nephrological Center, Piraeus General Hospital, Piraeus, Greece*

Aspergillosis is a sporadic disease with a world-wide incidence. We report a case of aspergillosis of the prostate which presented as persistent prostatis and urethritis, exacerbated by antibiotics.

Case Report

A 50-year-old man presented with frequency of micturition, dysuria and perineal discomfort. Neither fever nor leukopenia was present. On clinical examination the prostate was enlarged and painful. He had not received steroid therapy and there were no other predisposing factors. Repeated cultures of the prostatic fluid after prostatic massage grew different types of saprophytic schizomycetes and *Aspergillus flavus* over a 2-year period. More than 10 cultures were taken and from these *Aspergillus flavus* was isolated 6 times. Urine cultures for bacteria and fungi were always sterile.

Mycology Techniques

The prostatic fluid, obtained by meticulous sterile methods, was cultured on Sabouraud's glucose agar, Littman oxgall and Czapek Dox medium. The specific botanic characteristics of the fungus were seen only in the specific cultures and not on direct microscopy of the specimen. Rapid growth on Sabouraud at room temperature was noticed. The early growth was off-white, velvety and rapidly became greyish-green. The colonies covered the whole surface of the culture medium which became bright yellow a few days later. The colonies on Czapek Dox medium were velvety and bright yellow.

The growth of culture material began as a fine filamentous surface growth, and soon conidiophores were produced which extended up from the surface. The tips expanded into vesicles which produced numerous sterigmata over the surface, each with a long chain of spherical spores from its tip. Under a low-powered microscope these were seen as solid dark spore heads but under high power the mass of spores was identified as chains of spores attached to sterigmata arising from the central vesicle.

The patient had a prostatectomy and tissue sections of the prostate showed a marked acute and chronic inflammatory reaction with numerous giant cells containing septate filamentous hyphae. They were seen in haematoxylin and eosin stains. Scattered areas of necrosis were seen.

Comment

Aspergillus species may cause secondary infections in patients on immunosuppression, on prolonged antibiotic therapy or in patients with burns. They are also known to be involved in subcutaneous and generalised infections. Species of *Aspergillus* rarely infect healthy individuals such as our patient. They are usually opportunistic invaders which in recent years have become second only to *Candida* in frequency.

Aspergilli are often found as contaminants and it is always necessary to prove that they are the aetiological agent. If material is obtained by sterile methods and a pure growth of numerous colonies occurs, one can assume it is pathogenic. *Aspergillus* is often a slow-growing pathogenic organism, so that a selective medium such as Littman oxgall agar should be used in the primary isolation.

This was an unusual case of prostatitis in an apparently healthy man and we suggest that the diagnosis could be missed if there is not a high index of suspicion (Coudert, 1955).

Reference

Coudert, J. (1955). *Guide Pratique de Mycologie Médicale.* Paris: Masson

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Leiomyosarcoma of the Spermatic Cord

P. M. BUCKLEY, *Department of Urology, St James's Hospital, Leeds* and D. A. TOLLEY, *Department of Urology, Royal Infirmary, Edinburgh*

Case Report

A 65-year-old Caucasian male presented with a gradually enlarging, painless lump in the scrotum. On examination there was a firm, nodular mass adjacent to the left epididymis, which was thought to be cystic. This was explored through a left scrotal incision under local anaesthesia. A discrete, firm, nodular mass 3×2 cm arising from the spermatic cord was removed. Histology showed this to be a completely excised leiomyosarcoma of the cord (Fig.). He was readmitted and a left orchiectomy with high ligation of the cord was performed through a groin incision. An ellipse of scrotal skin from the site of the previous surgery was also excised. Subsequent histology confirmed that the previous excision had been complete.

Comment

Leiomyosarcoma of the spermatic cord is a rare, highly malignant tumour. Radical orchiectomy is the primary treatment of choice, as local recurrence from inadequate excision is common (Arlen *et al.*, 1969). The role of adjuvant therapy is less clear. In the majority of cases spread is haematogenous (Lundblad *et al.*, 1967). Radiotherapy is of little value as lymph node metastasis is uncommon and recurrent tumour is notoriously radio-resistant (Weitzner, 1973). The use of chemotherapy has been so limited that it is impossible to assess its role.

Acknowledgement

We wish to thank Mr Philip Smith for permission to report this case.

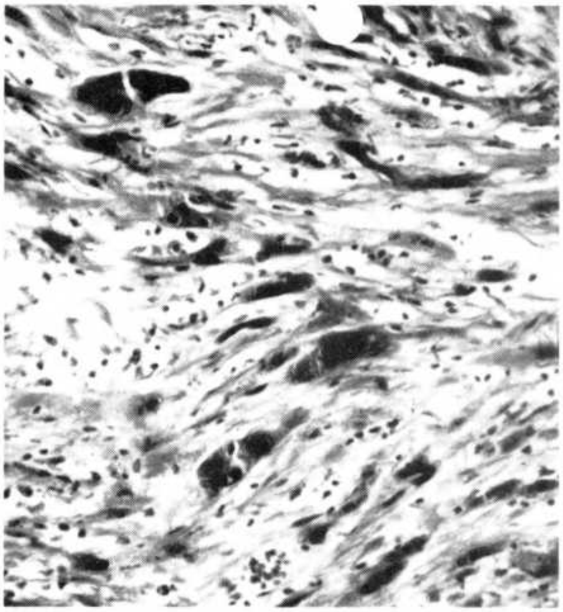

Fig. Photomicrograph of leiomyosarcoma (H and E ×75).

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A Mechanical Drip-stand for Use in Endoscopic Surgery

M. R. BUTLER, ANN MURRAY and P. D'ALTON, *Urological Departments, St James' Hospital and Meath Hospital, Dublin; Building and Engineering Department, St James' Hospital, Dublin*

The advantages of 3-litre bags of glycine to a practising urologist are obvious. However, in order to suspend them, the bags must be hoisted 6 to 8 ft into the air. The task of lifting these bags is often the lot of a junior nurse, and the spectacle of a nurse standing on an unsteady stool, struggling to hang 6 litres of glycine, can be very unnerving. To help our nursing colleagues, we have designed the following mechanical lifting apparatus (Fig.).

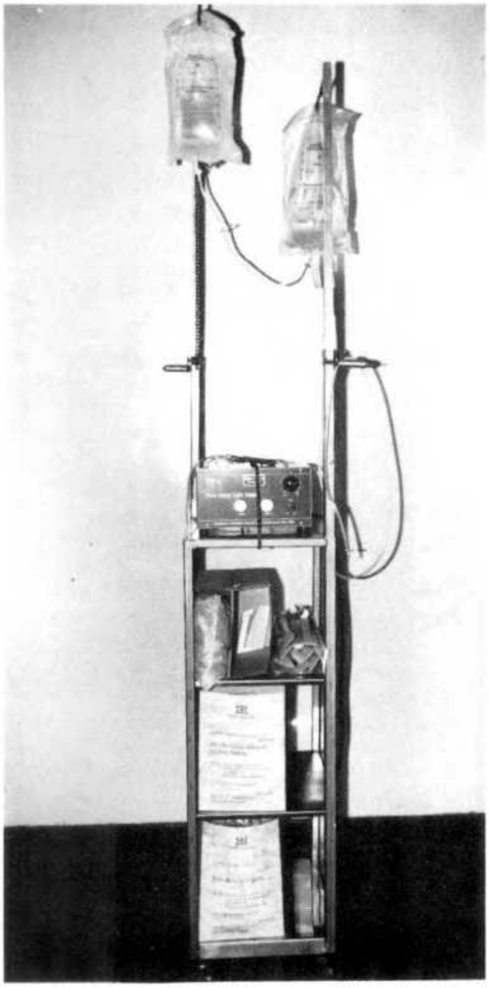

Fig. Shows the storage cabinet, with the vertical lifting mechanism and glycine packs in position.

The apparatus has 2 separate parts. The base is essentially a metal cabinet in which we store glycine packs for use during endoscopic procedures. In addition we store irrigation and IV sets. The cabinet is mounted on castors. The weight of the glycine packs stored in the base of the cabinet has the effect of stabilising the whole apparatus.

Lifting Mechanism

A vertical lifting mechanism is attached to the base of the cabinet, one on each side. It consists of a horizontal hanging arm for the glycine packs which is attached at right angles to the lifting mechanism. This mechanism is raised or lowered by an independently operated Simplex chain which is activated by a simple torque winding handle. The winding handle consists of 2 Simplex sprockets, and incorporates locking pins for positioning fluids at the required height.

During use one pole should be slightly higher than the other, so that the higher bag is a "feeding" bag. This bag maintains a supply of glycine to the lower bag, which, in turn, is connected to the patient. Hence the feeder bag can be changed with no break in the supply of glycine, and no interruption of the surgical procedure.

The cost of making this apparatus (the parts for which are available in many hospital workshops) would be approximately £180.00.

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Primary Mucinous Adenocarcinoma of the Renal Pelvis

R. M. WILD, JUN., L. E. LADAGA, J. S. COPELAND and P. F. SCHELLHAMMER, *Medical Center Hospitals, Departments of Urology and Pathology, Eastern Virginia Medical School, Norfolk, Virginia, USA*

Transitional cell epithelium may undergo squamous and glandular metaplasia in response to chronic irritation. Squamous metaplasia and squamous cell carcinoma is more usual but metaplasia to a columnar epithelium may occur and progress to adenocarcinoma (Mostofi, 1954). Mucinous adenocarcinoma of the renal pelvis ranks among the rarest of genitourinary malignancies. Arteriography has not been performed in previously reported cases. We report a case of mucinous adenocarcinoma recognised as malignant on the basis of an abnormal renal arteriogram.

Case Report

J.J., a 74-year-old black male, presented with a one-year history of gross haematuria, stringy mucoid urine and right loin pain. Examination revealed right flank tenderness and urine analysis demonstrated microhaematuria. Bloody efflux was noted from the right ureteric orifice. Plain X-ray of the abdomen showed a right lower pole staghorn calculus and a 1 cm calcified density in the upper pole. An infusion nephrotomogram revealed a right upper pole renal mass. Renal angiography showed changes consistent with neoplasm. Pre-operative diagnosis was renal carcinoma with an associated staghorn calculus.

Transabdominal radical nephrectomy and node dissection were performed. Macroscopic examination revealed that the pelvic mucosa was completely replaced by a mucoid papillary mass. Microscopic study demonstrated mucinous adenocarcinoma arising from the renal pelvis (Fig.).

Comment

In a previous review of the literature 32 cases of primary mucinous adenocarcinoma of the renal pelvis were reported (Aufderheide and Streitz, 1974). Renal calculi, hydronephrosis, pyelonephritis, and non-function are the common associated findings. Pain, haematuria and mucin production are usually present.

A pre-operative diagnosis of adenocarcinoma of the renal pelvis is infrequently made (Arcadi, 1956; Suzuki and Milam, 1967). This is the first report of an angiographic study and it clearly demonstrated neoplasm. The angiographic picture was one of neovascularity, whereas squamous and transitional carcinomas of the renal pelvis characteristically lack significant neovascularity (Cummings *et al.*, 1975). The renal parenchyma is often invaded by mucinous adenocarcinoma.

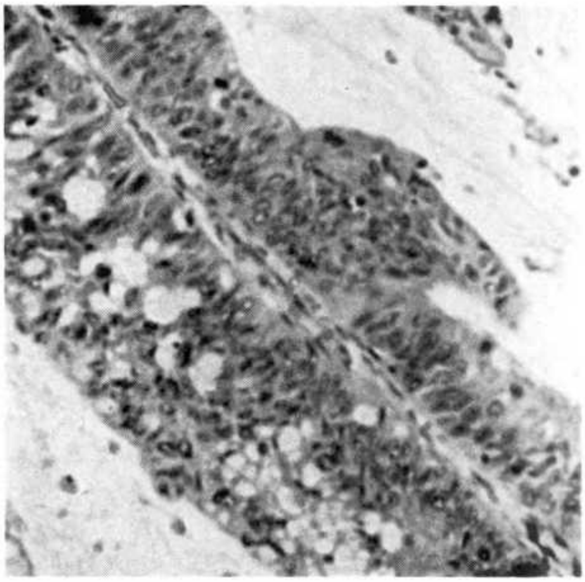

Fig. Photomicrograph of renal pelvis demonstrating normal transitional epithelium with adjacent papillary adenocarcinoma containing globulets of mucus (× 100).

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Points of Technique

Ultrasound Guided Suprapubic Puncture—A New, Simple Way of Releasing a Blocked Foley Balloon

M. REES, FRCS, *Surgical Registrar* and A. E. A. JOSEPH, FRCR, *Consultant Radiologist, Department of Nuclear Medicine and Ultrasound, St George's Hospital, Blackshaw Road, London SW17 0QT*

A new, safe method is described for releasing a non-deflating Foley balloon urinary catheter using ultrasound guided suprapubic puncture.

Local anaesthetic is infiltrated in the midline suprapubically and the catheter balloon then wedged at the internal meatus by gentle traction. The balloon is then located (Fig. 1) using a B mode ultrasound scanner equipped with a special transducer which has a central canal through which a needle may be guided. These transducers may be sterilised and are routinely used in ultrasound guided biopsies. Acoustic coupling between skin and transducer is obtained by using sterile lubrication jelly. The depth of the balloon may be measured by the B scan calipers and a needle inserted (Fig. 2). The advance of the needle may be followed on the A scan and balloon puncture coincides with an audible "pop".

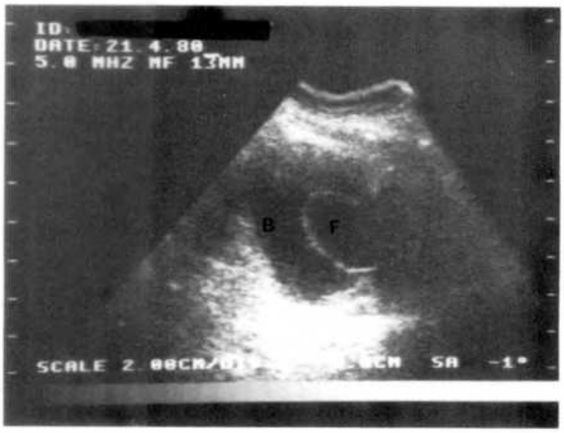

Fig. 1 Longitudinal scan showing Foley balloon (F) in bladder (B).

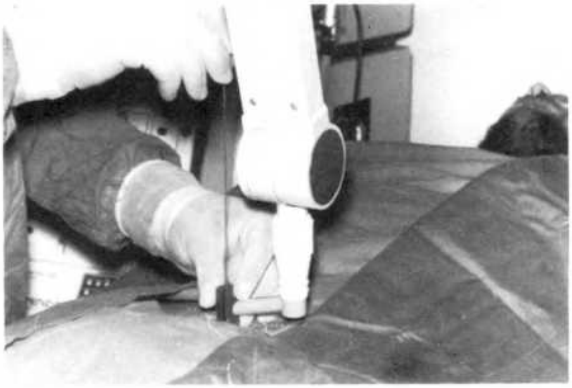

Fig. 2 Showing needle positioned in transducer canal.

Comment

Deflation of a blocked Foley balloon has attracted many original ideas, though we agree with Moisey and Williams (1980) that suprapubic puncture is the only safe, reliable method. They have advocated X-ray control as a useful technique for localising the balloon but, in our experience, ultrasound guided puncture is both simpler and quicker, with the specific advantage that screening could be in progress as the needle is advanced.

Reference

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Bloodless Lower Pole Surgery Without Vascular Clamping

J. TOSTAIN, *Department of Urology, Hôpital Bellevue, Saint Etienne, France*

The problem of vascular control during surgical procedures on the lower pole of the kidney may be approached in different ways. During urolithiasis surgery, nephrotomy or inferior heminephrectomy, the technique of kidney pedicle clamping provides perfect operating conditions but many surgeons are reluctant to impose unnecessary ischaemia on healthy renal tissue. On the other hand, incisions into renal tissue without clamping cause considerable blood loss and attempts to limit this loss by compression immediately above the cut encumbers the operating field and monopolises the operating hand.

To avoid these disadvantages the author uses a parenchymal clamping technique which is simple, atraumatic, does not prolong operating time and requires no special instruments.

The first step consists in locating the neck of the lower caliceal group using an intra-sinusal dissection. A safety loop may be placed around the kidney artery and vein beforehand, but is not absolutely necessary. A Vesseloop (size Maxi) (Medgeneral Lab, Minneapolis, Minnesota, USA), currently used for vascular occlusion, is slipped between the middle and inferior calices (Fig. 1a) and then tightened using a small haemostat (Fig. 1b). The amount of traction to apply is a matter of experience but can be judged easily.

Efficient renal parenchymal clamping is thus obtained. The technique is easy, completely atraumatic and is precise enough to be placed close to the area to be sectioned. During inferior heminephrectomy it is necessary to ensure separate haemostasis of the posterior branch of the renal artery. The tissue may then be cut using a scalpel. No bleeding will occur if proper traction is applied. Haemostasis of the visible arteries and veins on the cut surface is then carried out (Fig. 1c). After the primary haemostasis is completed the loop is slackened and any remaining bleeders are tied. The Vesseloop is removed, leaving a bloodless field. The rest of the operation is then completed. There are 3 advantages to this technique:

1. It is simple and does not lengthen operating time.
2. It is precise and limits ischaemia to that part of the organ to be cut or removed.
3. It is versatile and allows for a gradual unclamping and makes possible a stepwise haemostasis of smaller and smaller blood vessels.

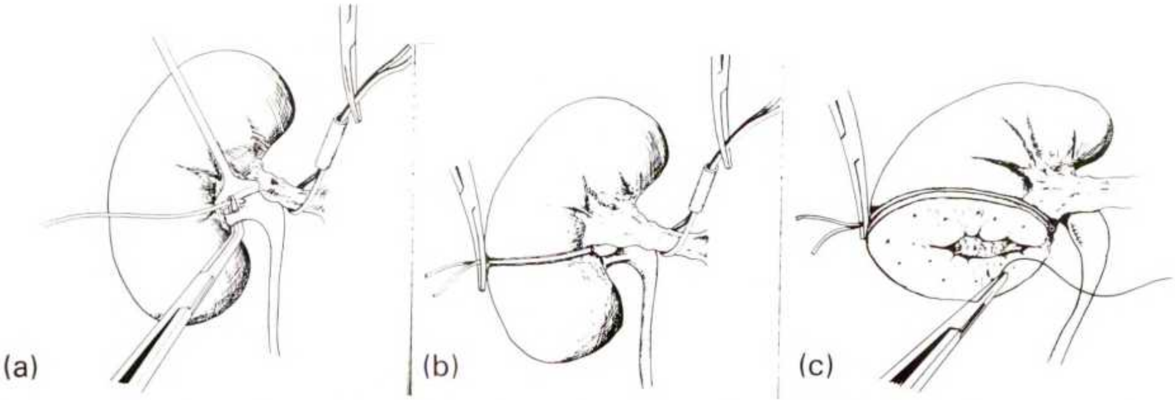

Fig. 1 (a) A Vesseloop is slipped between the inferior and middle calices. (b) The Vesseloop is tightened 5 mm above the part of the kidney to be removed. (c) Haemostasis is carried out on a bloodless slice.

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New Equipment

Intermittent Self-catheterisation: a New Instrument

C. L. A. H. BRUIJNEN, *Consultant Urologist, Catharina Hospital, Eindhoven* and P. W. BOER, *Professor in Urology, State University, Groningen, The Netherlands*

In 1972 Lapides *et al.* described clean intermittent self-catheterisation as an easy practical method for handling many types of lower urinary tract dysfunction.

To instruct women in self-catheterisation we designed a new instrument in 1976 (Fig.) (Bruijnen and Boer, 1980). A stainless steel mirror was applied to a classical stainless female 18 FG catheter. In this way it is possible for the patient to see her urethral meatus. A small disc prevents the bladder from perforation if it should be empty.

The patient stands facing the toilet with one foot on the toilet seat, and while spreading the labia with one hand she can catheterise herself with the other. After a few weeks she can catheterise herself without looking in the mirror, because she has learned where her urethral meatus is situated. This will give her the confidence to use a disposable catheter instead of a steel one. Careful hygiene is necessary. The catheter should be rinsed with water and dried. Once or twice a week it should be boiled in water and some vinegar.

This catheter is used successfully in both of our urological departments.

Acknowledgements

We are grateful to Mrs A. T. Brons-de Vries of the Urological Out-patient Department, to Mr S. Bosscher of the Technical Department of the University Hospital, Groningen, and to Mr W. Dekkers from the Technical Department of the Catharina Hospital, Eindhoven, for their help and assistance.

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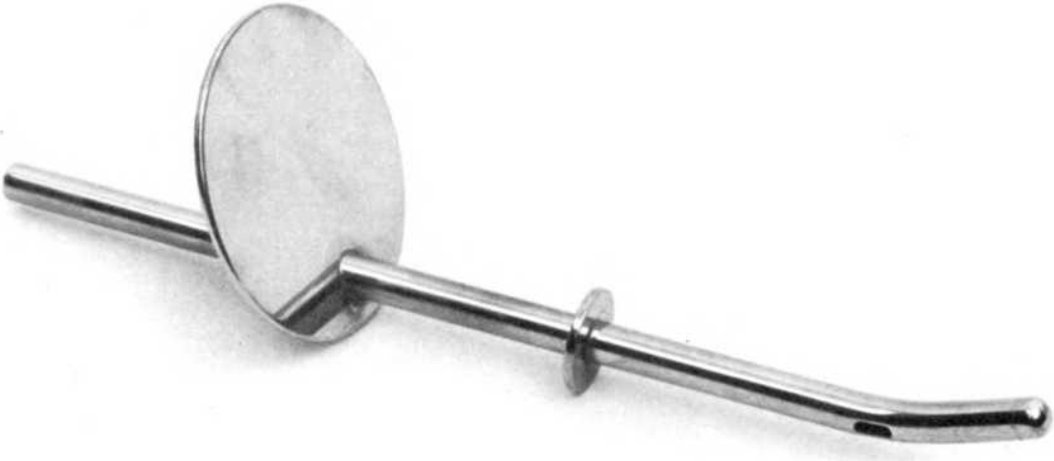

Fig.

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Notices

British Association of Urological Surgeons

PRESIDENT: W. K. YEATES

Annual Meeting: London, 8-10 July 1981

Further information from: J. L. Williams, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Institute of Urology in Association with The London Hospital Medical College

Endoscopic Surgery in Urology

29 April-1 May 1981

The course will be illustrated by the television transmission of operations supplemented by video recordings.

Topics will include the endoscopic management of benign and malignant prostate enlargement, strictures, stones and tumours occurring in the lower urinary tract.

Fee: £60.

Application forms and further details from the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01-836 5361.

Institute of Urology in Association with the Institute of Cancer Research

International Seminar on Diagnosis and Treatment of Germ Cell Tumours

29-30 May 1981

Topics: Recent advances in the pathological classification. Reappraisal of current status of surgical, radiotherapeutic and chemotherapeutic treatments of testicular and non-testicular germ cell tumours.

Speakers: J. P. Blandy, J. Donohue, L. Einhorn, E. Fraley, H. F. Hope-Stone, T. J. McElwain, B. Norgaard Pedersen, M. J. Peckham, M. L. Samuels, N. E. Skakkebaek, M. H. Tattersall, W. F. Whitmore.

Fee: £50.

Application forms and further details from the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01-836 5361.

Institute of Urology (The University of London)

Course on Operative Urology

1-5 June 1981

During this 5-day non-residential course operative procedures will be demonstrated by video and closed circuit television and techniques and cases discussed.

Topics: Conservative renal surgery, paediatric urology, reconstructive surgery, andrology, urothelial malignancy.

Speakers: Professor W. De Sy, Professor M. Marberger, Mr J. P. Pryor, Mr P. G. Ransley, Mr P. R. Riddle, Mr R. T. Turner-Warwick, Mr J. E. A. Wickham.

Fee: £100.

Further details and application forms from the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01-836 5361.

The course has been approved under the Advanced Postgraduate Training Scheme.

Athenian Days of Urology

Athens, Greece. 9-10 May 1981

The subject of the discussion will be "What's New in Urology?". Further information from: Professor C. Dimopoulos, University of Athens, Urological Department, King Paul's Hospital, Goudi, Athens, Greece.

Eighth International Course of Urology

Barcelona, Spain. 22-26 June 1981

Further information from: Professor J. M. Gil-Vernet, Catedra de Urologia, Hospital Clinico y Provincial, Casanova, 143, Barcelona 11, Spain.

Nato Advanced Study Institute on Cancer of the Prostate and Kidney

Erice, Sicily. 2-12 June 1981

Further particulars from: Professor M. Pavone-Macaluso, 9 Via Villa Trabia, 90141 Palermo, Italy, or Mr P. H. Smith, Department of Urology, St James's University Hospital, Leeds LS9 7TF.

Organisers wishing to have details of their courses and conferences published in the Journal should send details to J. E. Newsam, Western General Hospital, Edinburgh EH4 2XU.

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Book Review

Abdominal Ultrasound. Static and Dynamic Scanning. H. H. Holm, J. K. Kristensen, S. N. Rasmussen, J. F. Pedersen, S. Hancke, F. Jensen, J. Gammelgaard and E. H. Smith. Second edition. Pp. 274. Copenhagen: Munksgaard, 1980. Price D.kr. 300.00.

The increase in length of the second edition of this now multi-author text barely reflects the exponential advances in both the technology and applicability of ultrasound that have occurred since the publication of the first edition. In attempting to cover both obstetric and non-obstetric fields the authors have, in many areas, been forced to extreme brevity; this, however, is not always a bad thing.

Despite the re-writing of much of the original material, the addition of several completely new chapters and the replacement of all of the old bi-stable pictures with grey scale counterparts, the book still engenders a strong feeling of déjà vu and herein lies its strength, for once again there is a strong emphasis on cross-sectional normal anatomy, an essential prerequisite in this discipline.

For the urologist, the chapters covering the urinary tract are concise and contain a number of useful references. Other chapters which should prove of interest include the setting up of an ultrasound department, ultrasonically guided percutaneous puncture techniques, paediatric ultrasound and the relationship between ultrasound and CT scanning.

This book now provides a good introduction to the subject of abdominal ultrasound. The format is pleasant, with the easily read text being complemented by many good line drawings and grey scale images.

Books Received

Renal and Electrolyte Disorders. Edited by R. W. Schrier. Second edition. Pp. xii + 624. Boston: Little, Brown & Co., 1980. Price US $26.50: £13.80.

Hemoperfusion: Kidney and Liver Support and Detoxification, Part 1. Edited by S. Sideman and T. M. S. Chang. Pp. vi + 473. Washington, New York, London: Hemisphere Publishing Corporation, 1980. Price $49.50.

Tumeurs du Rein. (Monographies d'Urologie.) Edited by L. Boccon-Gibod and A. Steg. Pp. 126. Paris: Expansion Scientifique Française, 1980. Price 100 F.

Urolithiasis 3. (Der Kalzium-Oxalat-Stein.) R. Hautmann and W. Lutzeyer. Pp. 66. Berlin, Heidelberg, New York: Springer-Verlag, 1980.

Urolithiasis 4. (Der Kalzium-Phosphat-Stein.) J. M. Baumann, M. A. Dambacher, H. G. Haas, H. Sommerkamp and G. Rutishauser. Pp. 72. Berlin, Heidelberg, New York: Springer-Verlag, 1980.

Urolithiasis 5. (Der Harnsäure-, Zystin-, Xanthin-Stein.) D. Bach, R. Hartung, A. Hesse, W. Hicking, P. Leskovar, B. Lux, P. May, W. Schneeberger and W. Vahlensieck. Pp. 70. Berlin, Heidelberg, New York: Springer-Verlag, 1980.

Purine Metabolism in Man—III. Clinical and Therapeutic Aspects. (Advances in Experimental Medicine and Biology, volume 122A.) Edited by A. Rapado, R. W. E. Watts and C. H. M. M. De Bruyn. Pp. 444. New York: Plenum Press, 1980. Price US $45.00.

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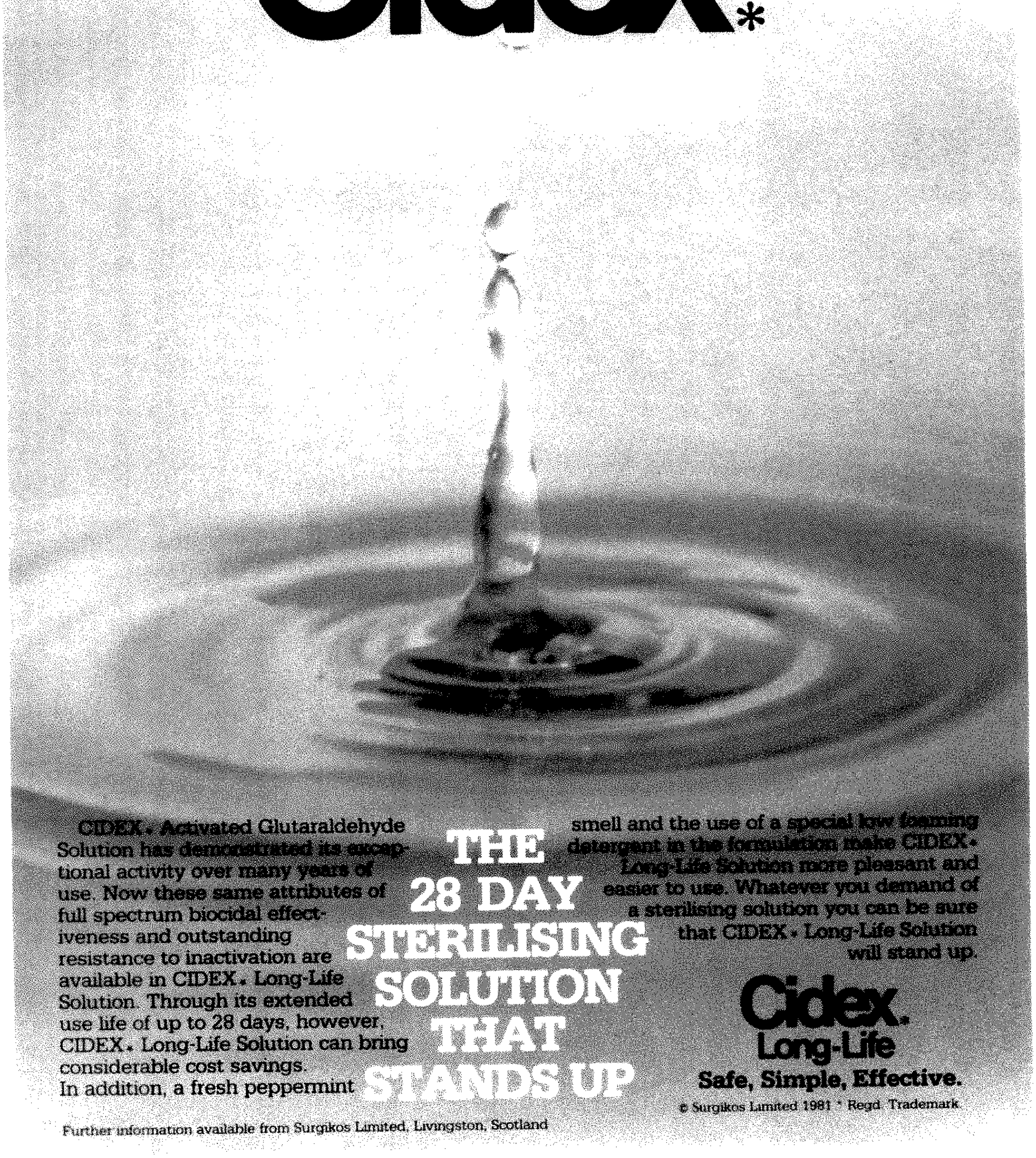

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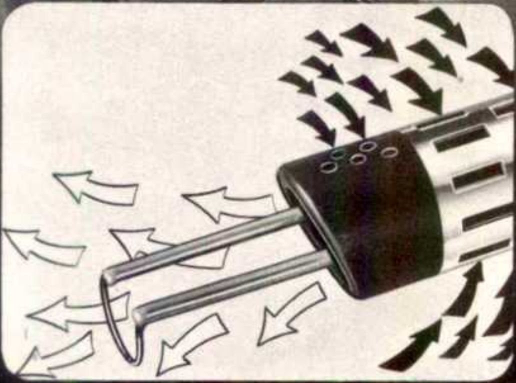

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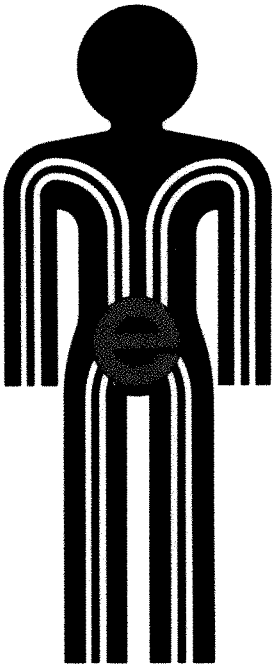

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1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer. E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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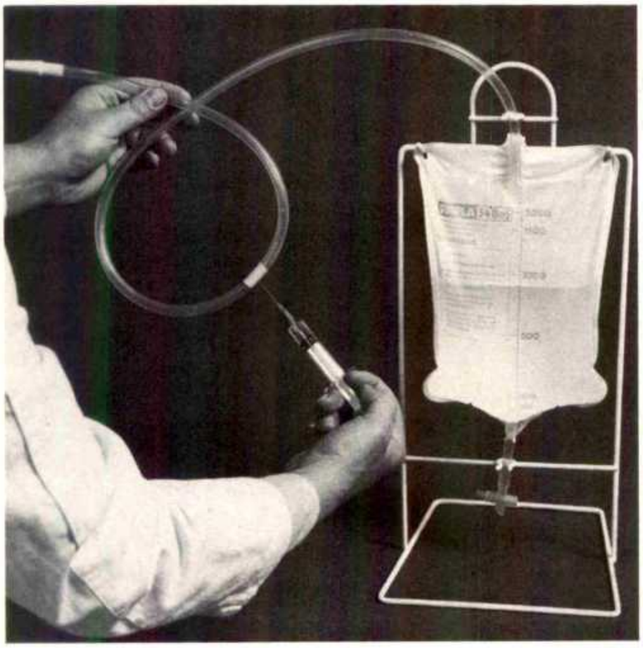

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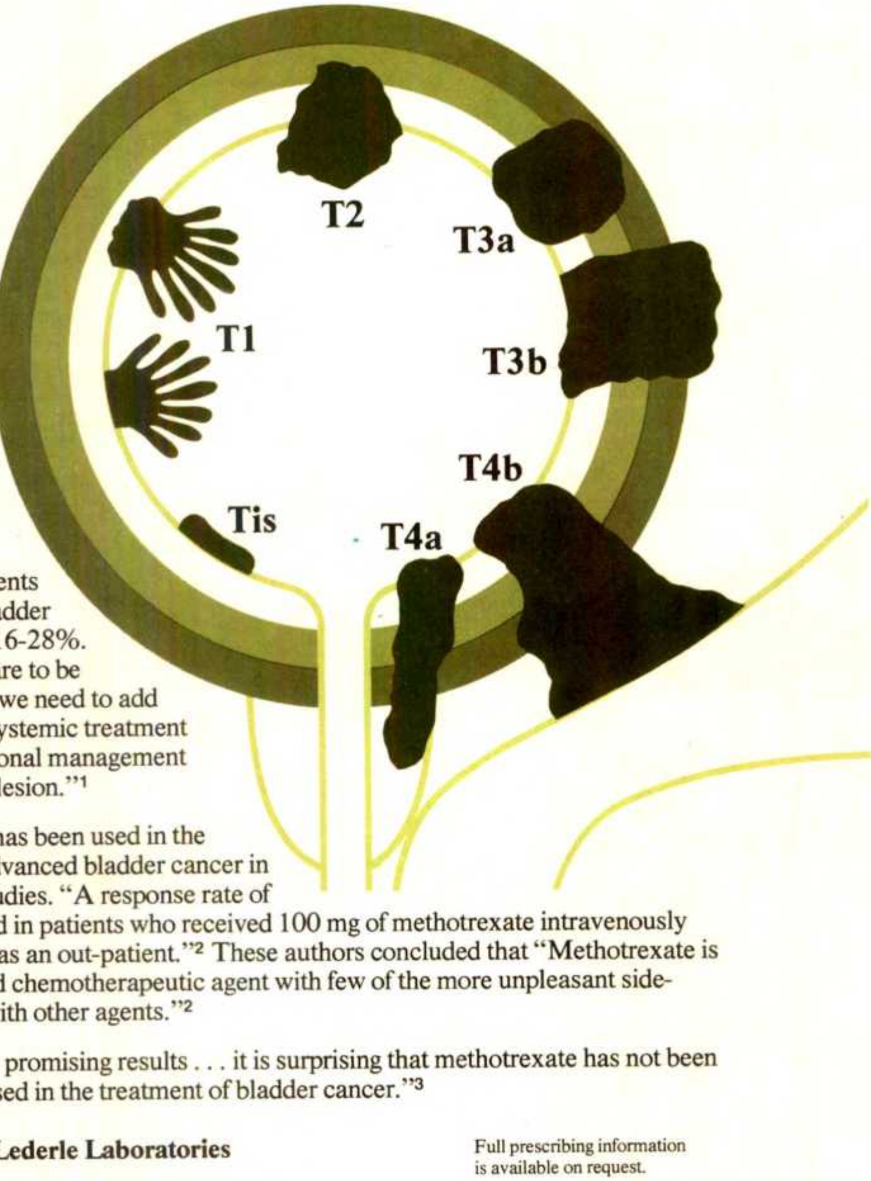

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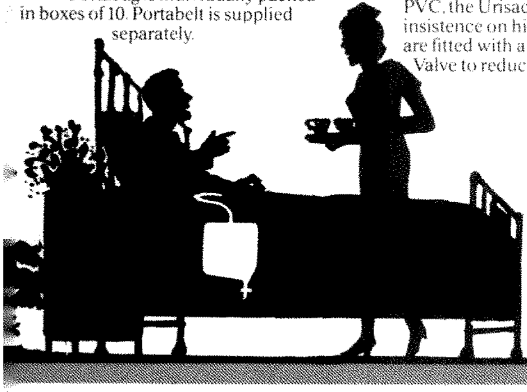

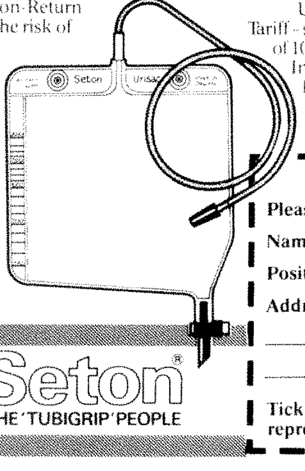

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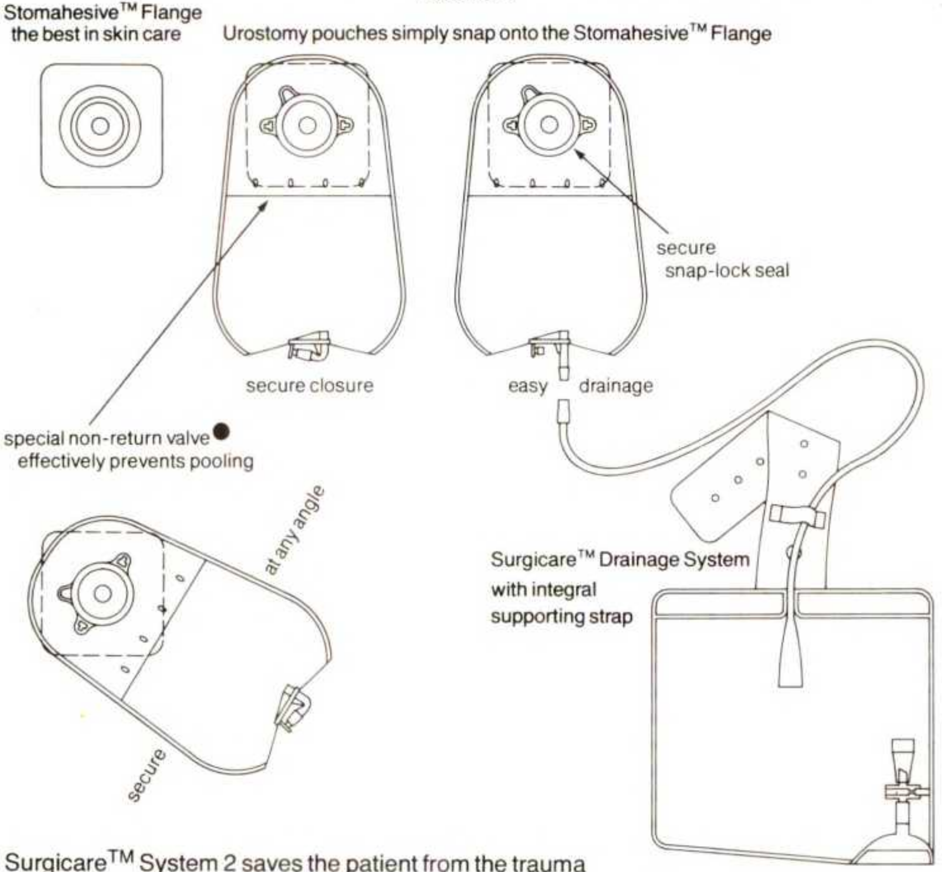
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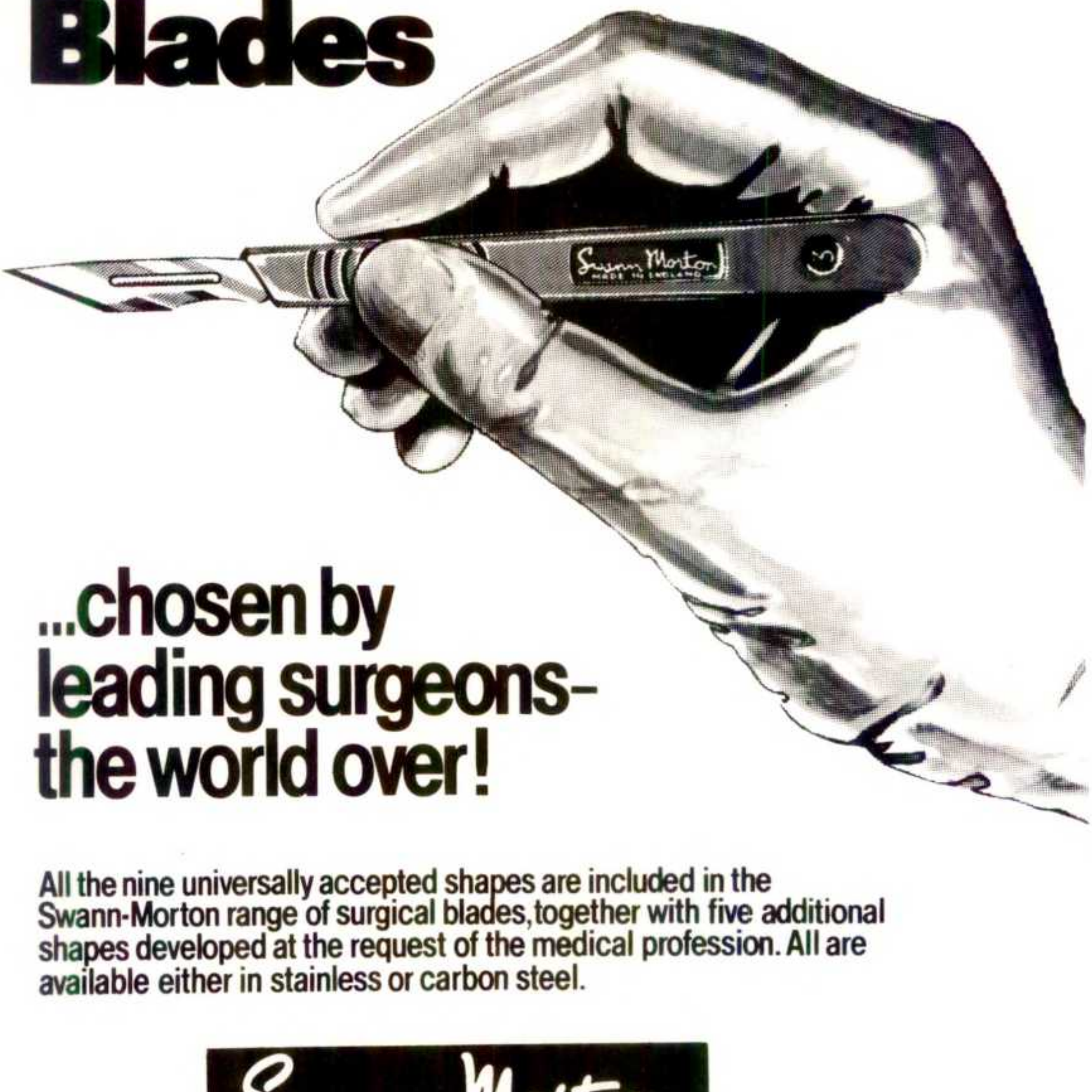

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Anterior Transperitoneal Approach for Stone Removal in Horseshoe Kidneys (its Advantage for Bilateral Stones)

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Summary—The anterior transperitoneal approach for removal of stone from a horseshoe kidney is described. The valuable advantages inherent in this technique have been shown in 13 patients, 7 with unilateral calculus and 6 with bilateral calculi, and all with horseshoe kidneys.

No urinary leak occurred and the post-operative course was uneventful. The operative field is extensive and a good exposure of both sides of the horseshoe kidney can be obtained, enabling bilateral pyelolithotomy or other conservative renal procedures to be performed.

The anterior transperitoneal approach to remove renal stones was suggested by Poutasse in 1961 and more recently by Linke *et al.* (1978). However, there have not been many followers so far and most urologists are reluctant to use this incision, mainly for fear of an intraperitoneal urinary leak. In the present paper we report our experience with this approach for the treatment of urolithiasis in horseshoe kidneys either for unilateral or for simultaneous bilateral stone removal.

Patients and Methods

During the last 3 years (1976-1978) 26 patients with horseshoe kidney were admitted to our department for symptoms due to nephrolithiasis. The surgical approach in the first 13 patients was the classical extraperitoneal horizontal flank incision and the procedures were 2 heminephrectomies, one Culp pyeloplasty, 8 pyelolithotomies and, in 2 patients, combined pyelolithotomy and nephrolithotomy.

In the remaining 13 patients who constitute the subject of this paper, the horseshoe kidneys were approached transperitoneally for the removal of the renal calculi. The stones were unilateral in 7 patients and for these there were 4 right pyelolithotomies, 2 left pyelolithotomies and one patient had a Culp pyeloplasty as well as a lithotomy. All of these were single calculi.

Of the 6 patients who had bilateral procedures, 5 had stones on both sides and one patient had a stone removal on one side with pyeloplasty and at the same time a pyeloplasty performed on the opposite side. In 4 of the patients the stones were not only bilateral but also multiple on one or both sides and 3 of these patients had been subjected to previous pyelolithotomy by the loin approach.

Surgical Technique

The patient was placed on the operating table in the hyperextended supine position. A long pararectal incision can be extended upwards as far as the xiphisternum if necessary (Fig. 1). After displacing the omentum and small intestine medially, the ascending colon was freed by dividing the

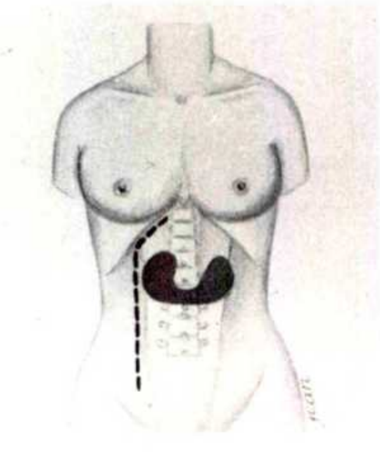

Fig. 1

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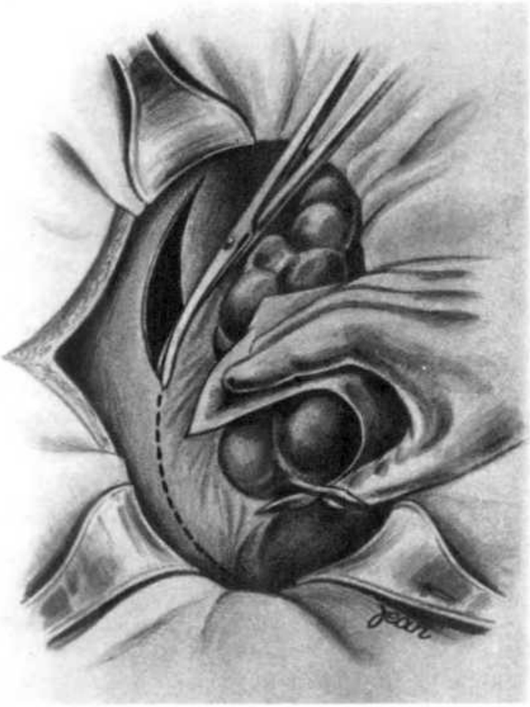

Fig. 2

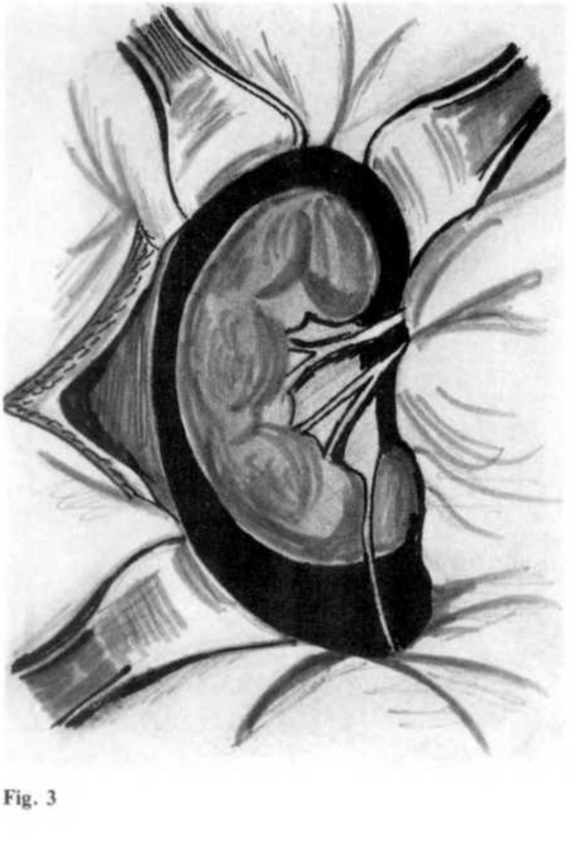

Fig. 3

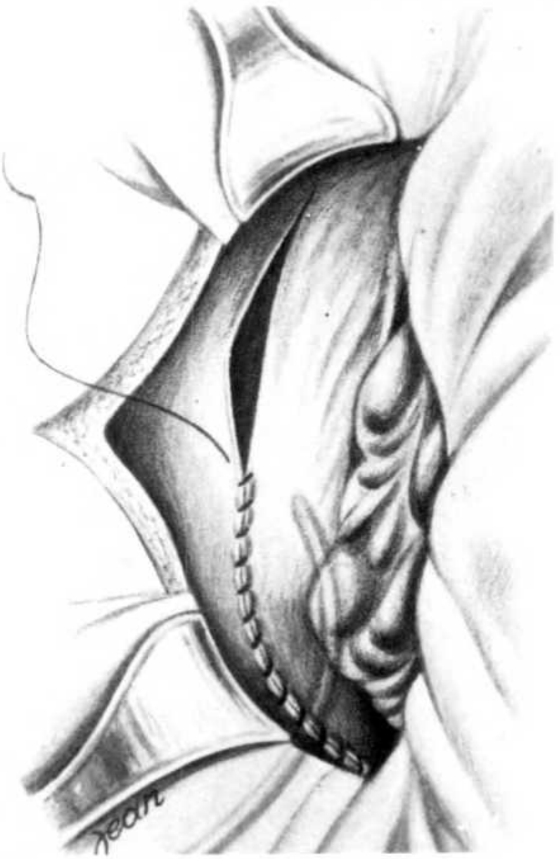

Fig. 4

peritoneum lateral to the colon and was mobilised medially by blunt disection (Fig. 2). The retroperitoneal exposure was excellent and the upper ureter and right side of the horseshoe kidney including the isthmus could be seen (Fig. 3). The renal pelvis could then be disected and the surgical manoeuvre of choice performed. This may be a pyelolithotomy, pyeloplasty, isthmic section or heminephrectomy. A drain was placed retroperitoneally and brought out through a stab incision in the flank. The ascending colon was replaced and the posterior peritoneum closed with a watertight continuous catgut suture (Fig. 4). The parietal incision was closed in the usual manner, using silk sutures for the aponeurosis.

For simultaneous bilateral operations the peritoneum was opened through a long transverse incision arching over the umbilicus from one flank to the other (Fig. 5). Both rectus muscles were divided transversely and the wound opened widely with a self-retaining retractor. The right renal pelvis was exposed as already described in the unilateral approach. For the left half of the

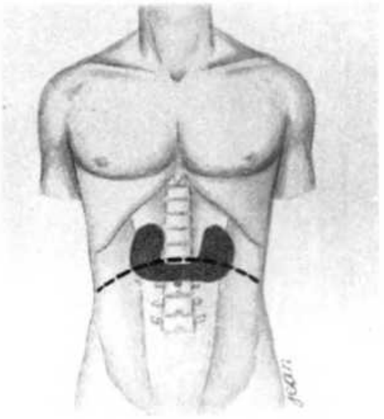

Fig. 5

horseshoe kidney the left colon was elevated and the posterior peritoneum incised down the left paracolic gutter (Fig. 6). The descending colon and intestines were displaced medially and superiorly by wet packs, exposing the left part of the renal horseshoe which was easily dissected. After drainage and closure of the posterior peritoneum with continuous absorbable sutures (Fig. 7) the intestine was replaced and the parietal wound closed, using mattress chromic catgut sutures for muscles and silk for the aponeurosis.

Results

The post-operative course was remarkably smooth. No urinary leaks were noted and all of the pelvic incisions healed by primary intention. Post-operative ileus was insignificant and no gastric tube suction was necessary. There was no clinical evidence of peritonitis. For the first 3 to 4 days the fluid requirements were given intravenously and the patients were encouraged to sit out of bed as soon as possible.

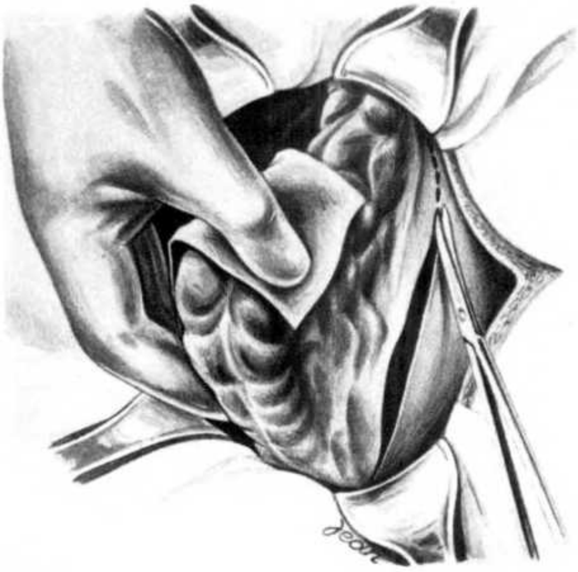

Fig. 6

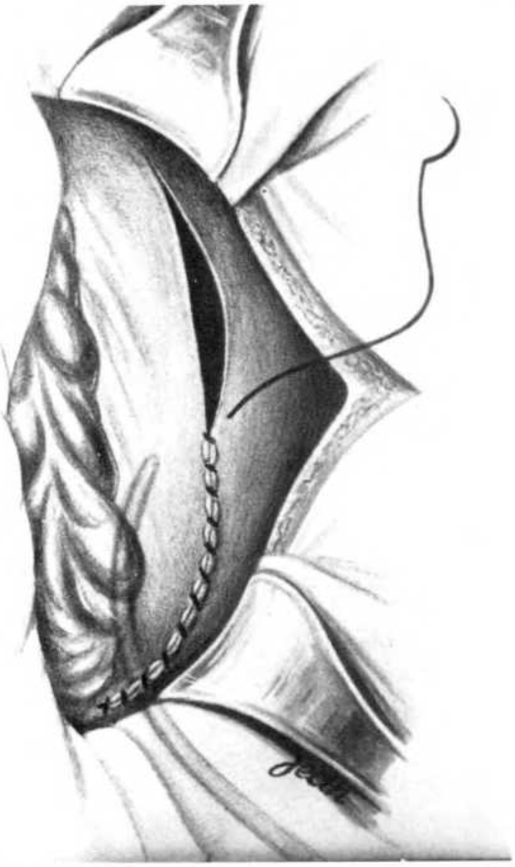

Fig. 7

In all but one patient stone removal was complete. One patient with heavily infected urine had an early recurrence of stone and may require removal of the left part of the horseshoe kidney in due course. The transverse scars were sound and no incisional hernia has been noted.

Discussion

The anterior transperitoneal approach has proved to be of great advantage in patients with nephrolithiasis in horseshoe kidney, particularly in those with bilateral disease.

The operative field is extensive and with a good self-retaining retractor the intestinal bulk is easily displaced and held away from the operative field. The renal pedicle is easily controlled because access to the vessels is good. Any form of conservative procedure on the kidney can be performed and the approach can be recommended for patients who have already had renal surgery and in whom previous adhesions would make a loin dissection difficult.

If the renal pelvis is closed meticulously there is no risk of an intraperitoneal urinary leak. The peritoneum on the posterior abdominal wall can be closed with a watertight suture provided there is adequate drainage to the flank. Access to a horseshoe kidney is easier because of the lower anatomical location. The transverse incision gives good exposure for both kidneys and avoids the need for a double loin approach when bilateral disease exists. The transperitoneal approach is also an advantage in patients who are very obese, as stone formers tend to be.

Stone removal in horseshoe kidneys can be performed routinely on either side or both sides through an anterior transperitoneal approach with obvious advantages. This technique deserves more attention than it has received in the past.

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The Dilated Non-obstructed Renal Pelvis

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Summary—This paper discusses 28 patients with renal pelvic dilatation in whom obstruction was excluded by excretion urography and diuresis renography. The clinical presentation and progress of the patients over a follow-up period of 1 to 5 years are presented. One patient required pyeloplasty, one developed 2 asymptomatic renal pelvic calculi and one showed some deterioration in function on the affected side.

The remaining 25 patients remain well and their follow-up renograms show satisfactory renal function and excretion. Before the advent of objective means of assessing renal function and urodynamics, these patients would probably have been subjected to pyeloplasty. The present study confirms that the correct management of the dilated non-obstructed renal pelvis is conservative.

Recent years have seen a radical reappraisal of the concept of the dilated renal pelvis. The early work of Whitaker (1973, 1976), using perfusion studies to measure pressure against flow across sites of suspected obstruction in the upper urinary tract, demonstrated that dilatation was not necessarily indicative of impedance to flow. With the development of diuresis renography to assess individual renal function and upper tract urodynamics (O'Reilly *et al.*, 1978, 1979), and radionuclide parenchymal transit times to evaluate obstructive nephropathy (Whitfield *et al.*, 1977), non-invasive methods to investigate and follow up these patients have become available.

In addition, histological and electron microscopy studies have demonstrated morphological differences between dilated obstructed and dilated non-obstructed renal pelves (Gosling and Dixon, 1978). While the former condition is an unequivocal case for surgery, the nature and management of the dilated non-obstructed renal pelvis have not been established. This paper presents an analysis of our experience with this condition over the past 5 years.

Patients and Methods

The series comprised 28 patients, 9 males and 19 females with an age range of 16 to 52 years (mean 36 years). All had intravenous urograms following their initial consultation and diuresis renograms after the urogram. They were then followed for a period ranging between 1 and 5 years (mean 2½ years). All had at least 6-monthly out-patient visits and 2 follow-up renograms. All patients were interviewed for the purpose of this study: 16 had additional ^{123}I-hippuran gamma camera renograms.

Excretion urography was performed in the standard manner without any special use of high dose contrast, provocative or diuretic modifications. Renography in the early days was performed using ^{131}I-hippuran and a probe system of scintillation detectors linked to a chart recorder. For the last 2½ years, ^{123}I-hippuran and a gamma camera computer system have been used. The technique of diuretic provocation has been reported before (O'Reilly *et al.*, 1978, 1979). Briefly, a standard renogram is performed, followed by a second renogram 3 min after the intravenous injection of 0.5 mg/kg of the diuretic frusemide. If the graph shows a rising curve on the initial renogram with tracer retention at 20 min, the frusemide is given in continuity to observe its effect on this rising curve. The technique has been shown to correlate well with other available methods of examination, including operative findings, parenchymal transit time studies and perfusion techniques (Koff *et al.*, 1979). It also correlates well with objective morphological changes in the affected renal pelvis (Lupton *et al.*, 1979). Simultaneous renal function is estimated by the 2-min hippuran uptake test, which has been shown to correlate well with con-

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

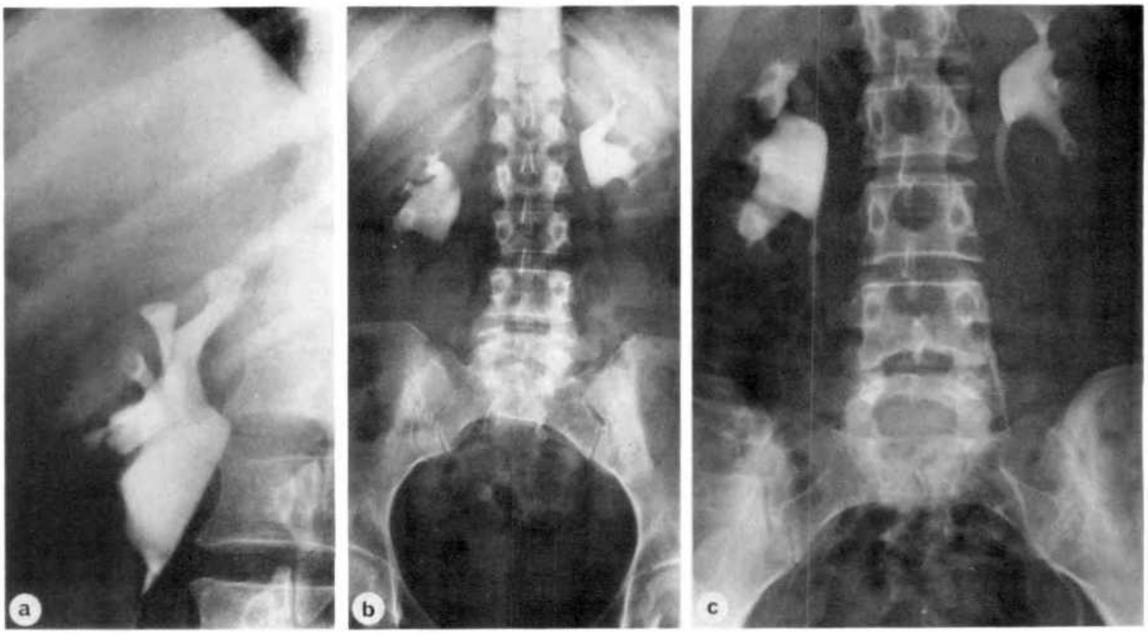

Fig. 1 (a) Non-obstructed dilated right renal pelvis. (b) Non-obstructed dilated bilateral renal pelvis. (c) Obstructed dilated right renal pelvis; non-obstructed dilated left renal pelvis.

stant hippurate infusion clearance and individual renal urine collections (Hayes *et al.*, 1974) and with ^{99m}Tc-DMSA renal fixation tests (Holten and Storm, 1979).

Results

Clinical Features

Twenty-five of the 28 patients were referred because of unilateral loin pain. Of these, 7 had pus cells in their urine, but there was no significant bacterial growth from any of the urine samples. Two patients were referred because of lower urinary tract symptoms of frequency and dysuria, and one complained of non-specific, recurrent colicky abdominal pain. Haematological and biochemical results were uniformly normal.

Excretion Urography

The urograms showed the same general appearances (Figs. 1a, b, c). Some dilatation of the renal pelvis was apparent on the side of the symptoms with a non-dilated or more often non-visualised ureter below. The pelvis often had a square configuration. The calices were often dilated but clubbing was absent in all but 3 patients. Cortical thickness was satisfactory except in 2 cases where there was polar thinning.

Diuresis Renography

All patients showed good bilateral renal function. In some, excretion was slower than normal or a little delayed (Fig. 2a). In all of these, when the test was repeated under diuresis, the curves reverted to normal (Fig. 2b). In the remainder, excretion on the affected side was initially absent. When frusemide was given in continuity, however, there was prompt, efficient and complete elimination of the tracer from the upper tract (Fig. 2c). This was accepted as the previously described picture found in the dilated, hypotonic, non-obstructed system.

In the light of these results, these patients were managed conservatively. This decision was further strengthened by the fact that during a previously reported study, 4 patients showing similar renograms underwent pyeloplasty. Histological and electron microscopy of the operative specimens, however, showed appearances indistinguishable from normal with none of the stigmata of idiopathic hydronephrosis.

Follow-up

Patients were followed at 6-monthly intervals. Several had been discharged after 3 years, but they were re-examined for the purpose of this study. All had at least 2 follow-up renograms at

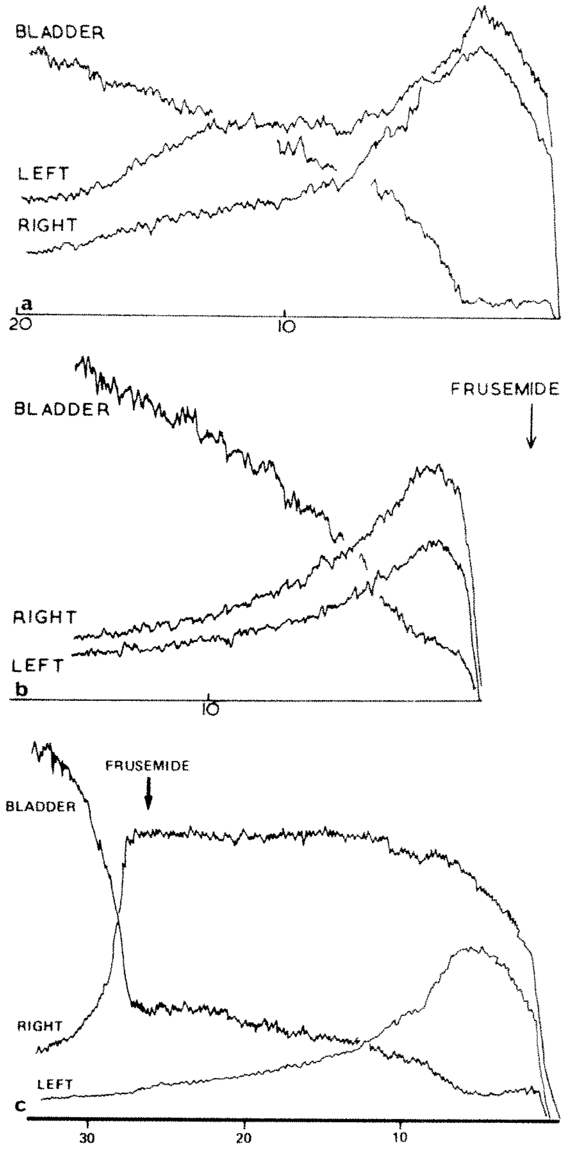

Fig. 2 (a) Sluggish renogram third phase suggesting partial obstruction of left kidney, but excellent function. (b) Renogram from same patient showing normal appearances under diuresis. (c) Initially rising renogram curve on right side suggesting obstruction converted to rapid prompt elimination pattern by diuresis, indicative of a dilated non-obstructive dilatation.

one year or more after the initial consultation; 16 have had repeat ^{123}I-hippuran gamma-camera studies within the last 12 months.

Progress

One patient remained symptomatic, complaining of loin pain 18 months after presentation. Her diuresis renogram was normal at first but later showed signs of decreasing function and equivocal obstruction. In view of this, she proceeded to pyeloplasty. Her post-operative studies are once again normal.

One patient, who initially complained of lower tract symptoms, developed 2 asymptomatic renal pelvic calculi. Although the urine occasionally showed 1 to 5 pus cells per high power field, there was no pattern of persistent or intermittent urinary tract infection.

The initial renogram in one patient showed normal appearances with equal patterns on both sides. Gamma-camera renography 3 years later showed function on the dilated side to be only 27% of the total; 6 months later this figure had risen to 36%. The urodynamic drainage curves are normal, she remains asymptomatic and will continue to be followed up conservatively.

The remaining 25 patients remain asymptomatic and became so within 12 months of initial consultation. Follow-up renograms show unchanged function and excellent elimination patterns. All remain under annual review.

Discussion

In the past, many patients with non-obstructive dilatation of the renal pelvis were undoubtedly judged to have pelviureteric junction obstruction and proceeded to possibly successful but completely unnecessary and potentially harmful pyeloplasties. Only in the last few years have methods become available to demonstrate that dilatation is not necessarily to be equated with obstruction and that the patient with a dilated non-obstructed renal pelvis or ureter will not necessarily benefit from surgery.

The current methods for assessing these patients include diuresis renography, radionuclide parenchymal transit times and pressure-flow perfusion studies. If a dilated, non-obstructed system is found, it is our policy to follow the patient's progress by repeated out-patient visits and interval diuresis renograms. This particular means of evaluation gives a rapid, non-invasive assessment of both differential renal function and upper tract urodynamics which correlates well with other established procedures and objective renal pelvic morphology. Parenchymal transit times give a good quantitative index of obstructive nephropathy but the technique is somewhat complex and does not give urodynamic information. Con-

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versely, the antegrade perfusion test does not measure function and is unsuited to repeated investigations if conservatism is decided upon. We now reserve these techniques for cases remaining equivocal after diuresis renography.

The decision for non-surgical management in this series has been supported by the results: 25 of the 28 patients (89%) became asymptomatic and showed no objective deterioration in renal function or excretion. However, these patients and the 3 who developed complications raise certain questions about the overall concept of idiopathic hydronephrosis:

What is the aetiology of non-obstructive renal pelvic dilatation? Non-obstructive dilatation of the ureter is well documented. In 1966 Shopfner described a series of patients with what he termed ureteric ileus or atony. He showed an infective aetiology in over half of these. It is known that acute infective episodes can result in dilatation of the renal pelvis and once established, such dilatation may persist from residual hypotonicity of the attenuated musculoelastic tissues. Other factors such as chronic vesicoureteric reflux, previously undetected but self-limiting episodes of obstruction from stones, or aberrant vessels might also produce the same result, initiating dilatation which persists after the provocative episode is resolved as a slightly dilated hypotonic pelvis.

Is such non-obstructive dilatation damaging to the kidney? It is probably true that the main threats to renal function in hydronephrosis are high intermittent intrapelvic pressures or infection. In the absence of these, the indication for operation is removed and conservatism is indicated. In this series, one patient was operated on for persisting symptoms and deteriorating objective investigations. The causes of loin pain are multiple and its presence should not automatically be assumed to be due to pelvic dilatation on the excretion urogram. Persistent symptoms are an indication for further investigation, but not necessarily for a pyeloplasty. One patient developed 2 asymptomatic renal pelvic calculi. The incidence of stones in this series is thus 3.6%. Stasis is inevitable in a dilated renal pelvis. Experimental work has shown that peristalsis may be ineffective in the normal renal pelvis at low flow rates. In a dilated system, even normal flow rates may be insufficient to propagate the peristaltic wave from the caliceal pacemakers, so allowing stasis to occur. The crucial point is whether stasis alone is sufficient to cause stones in these patients in the absence of infection. This does seem to have been the case in this patient. However, even after pyeloplasty, stasis may occur, and there is no evidence to suggest that pyeloplasty in the non-obstructed dilated pelvis will decrease the possibility of stone formation. The differential renal function in one patient deteriorated temporarily on conservative management. It subsequently improved and there is no evidence of obstruction. She continues to be followed and there is no objective indication for operation.

It is concluded that dilatation of the renal pelvis can occur in the absence of obstruction. Such cases should undergo objective evaluation and thereafter be managed conservatively. There is no evidence as yet to suggest that non-obstructive dilatation is a precursor of true pelviureteric junction obstruction. Diuresis renography provides a good screening and follow-up technique, but equivocal cases may require more detailed or invasive assessment. Such application of all the available procedures will result in a more logical approach to the problem of the dilated renal pelvis.

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Safeguarding the Kidney after Non-traumatic Perirenal Haemorrhage

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Summary—Three case reports of the unusual condition of spontaneous perirenal haemorrhage are presented and their management discussed. An early accurate diagnosis and a trial of conservative management is suggested rather than emergency surgery which usually results in nephrectomy.

Spontaneous haemorrhage from the kidney is a rare but established cause of abdominal apoplexy (Alderman and Murphy, 1959). An emergency laparotomy may lead to unnecessary nephrectomy, but modern investigation can substantiate the diagnosis, if suspected, and thereby avoid operation.

Case Reports

Case 1. A man aged 57 years was admitted with sudden severe right-sided abdominal pain, a pulse of 80 per min and BP 200/105 mmHg. There was marked tenderness and guarding in the right upper quadrant of the abdomen. Emergency laparotomy exposed an expanding right perirenal haematoma. Dissection traced the source of the bleeding to a 2 cm crater on the anterior surface of the kidney which was sutured and biopsied. Histology of the tissue was that of a simple renal cyst.

Case 2. A man aged 46 years presented after 24 h of severe left loin pain, a pulse of 120 per min and BP 170/125. Examination demonstrated tenderness in the left loin and a provisional diagnosis of ureteric colic was made. The next day a mass was noted in the left loin. Urography demonstrated upward and lateral displacement of the kidney by a large mass. The mass increased in size, the venous haemoglobin concentration fell and laparotomy was undertaken. The mass proved to be a perinephric haematoma. When the surgeon opened the perinephric fascia severe bleeding was encountered and was controlled only by nephrectomy. The kidney showed a 5 mm cortical renal infarct at the site of the haemorrhage.

Case 3. A 53-year-old man developed increasing left loin pain over a period of 8 h. He had previously been investigated for severe hypertension and had no function in his right kidney. The pulse was 52 per min and BP 160/90. Examination showed a large tender mass in the left loin. Emergency urography demonstrated a normal left kidney and a large soft tissue mass in the left loin. A clinical diagnosis of perirenal haemorrhage was made and subsequently confirmed by CAT scanning which proved the mass to be confined to the perinephric tissues (Fig.).

Arteriography showed normal renal vasculature and the patient was managed conservatively. Resolution of the haematoma was confirmed by repeat CAT scanning over several months.

Discussion

Non-traumatic perirenal haemorrhage is rare and seldom suspected clinically, although mentioned first by Wunderlich in 1856. Lenk (1909) described the 3 characteristic features of the syndrome: abdominal pain, flank mass and signs of internal

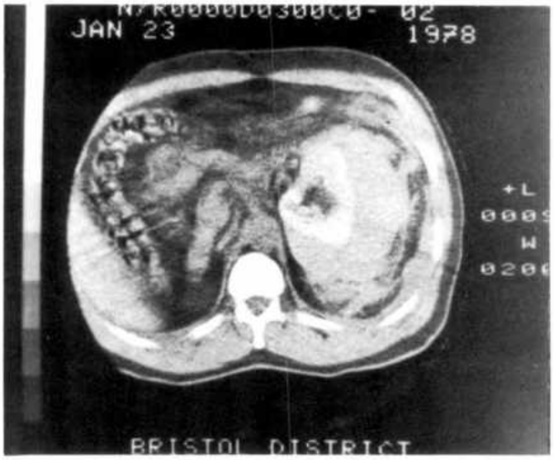

Fig. Safeguarding the kidney after non-traumatic perirenal haemorrhage.

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haemorrhage. There are many causes of perirenal haemorrhage but in at least 15% of cases no specific diagnosis can be made. It is a dangerous condition with a mortality of 30 to 40% (Uson *et al.*, 1959). There is also a risk of an "unnecessary" nephrectomy if a diagnostic laparotomy is undertaken.

There are 4 important categories in the syndrome of abdominal apoplexy; ruptured aortic aneurysm, intraperitoneal haemorrhage arising from a mesenteric vessel, adrenal apoplexy and perirenal haemorrhage. All have associations with hypertension. In 30% of cases the source of the haemorrhage cannot be identified (Kleinsasser, 1970). The clinical diagnosis of a ruptured aortic aneurysm is commonly made without difficulty. Mesenteric bleeding is usually from one of the second or third order branches of the aorta (Stevenson *et al.*, 1978). In these 2 categories laparotomy is essential because the bleeding is unconfined. Adrenal apoplexy is rare and the diagnosis is often missed (Miller, 1960) but it is equally important since there is a real risk to the kidney during exploration of a large suprarenal haematoma.

Haemorrhage from the renal parenchyma is initially confined by the strong layers of the perirenal fascia. It is suggested that the diagnosis of perirenal haemorrhage be considered in all cases of atypical abdominal catastrophies. If suspected and the condition of the patient is stable, investigation by urography, ultrasound, CAT scanning and visceral angiography are to be preferred to emergency laparotomy. Such investigations may allow conservative management to be continued until spontaneous resolution has occurred.

An intra-operative diagnosis of a perirenal haematoma presents a difficult problem in that on-table urography gives limited information, particularly in a hypotensive patient. We suggest that in the case of a non-expanding perirenal haematoma discovered at operation, the perirenal fascia should be left intact and the abdomen closed. If free bleeding is found at laparotomy the haematoma should be explored and an attempt made to identify and control the source of the bleeding since there is no alternative.

Non-traumatic haemorrhage from the kidney is rare and insufficiently recognised. It may account for some cases of abdominal apoplexy of unknown cause. Clinical awareness and full investigation should minimise the risk of arbitrary nephrectomy.

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Symptomatic Renal Angiomyolipoma

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Summary—Two cases of symptomatic renal angiomyolipoma not associated with tuberous sclerosis are presented. The clinical and radiological features, the pathology and the management of these rare but well documented tumours are briefly discussed. They pose problems in diagnosis and controversy still exists regarding their management. Recent radiological techniques such as CT may help in the diagnosis. When conservative surgery is not possible, or when an adenocarcinoma cannot be confidently excluded, nephrectomy should be performed.

A century has passed since Bourneville and Brissard first described renal angiomyolipoma. This rare but benign tumour is often difficult to differentiate from an adenocarcinoma. Angiomyolipoma is commonly seen in patients suffering from tuberous sclerosis but may occur in the absence of this disease. Two cases of angiomyolipoma apparently not associated with tuberous sclerosis are presented.

Patients

Case 1. A 54-year-old female was referred to the outpatient clinic with a 3-month history of right loin pain and dysuria. Two weeks previously she had passed a stone *per urethram*. General examination did not reveal any abnormality. Routine haematological and biochemical investigations were within normal limits. An intravenous urogram (IVU) demonstrated a normal right kidney but the appearances of the left kidney suggested a centrally placed space-occupying lesion which on ultrasound examination was found to be of solid consistency. Computerised tomography (CT) of the kidney confirmed the mass in this kidney, which was of low attenuation values compatible with fat, and a tumour predominantly of fat substance was reported (Fig. 1). The kidney was explored through a loin approach with a view to performing a frozen section biopsy. However, as the tumour was centrally located and extended into the pelvis, a simple nephrectomy was performed. There was no tumour in the renal vein and no enlargement of the regional lymph nodes.

The bisected kidney showed a soft, yellow, fatty mass 4 cm in diameter which distorted the calices and compressed the surrounding parenchyma (Fig. 2). Separate from the main tumour, in the subcapsular region, there was a firm nodule 0.5 cm in diameter. On histological examination the main mass consisted mostly of mature adipose tissue, but in places there were bundles and islands of smooth muscle cells. Thick walled, often hyaline blood vessels were also present. The small subcapsular nodule consisted of smooth muscle only.

Case 2. A 24-year-old female was admitted as an emergency to a District General Hospital with acute pain in the right hypochondrium. On admission she looked pale and unwell. She was apyrexial, pulse rate was 94/min and the blood pressure was 140/90 mmHg. There was diffuse tenderness in the upper abdomen with guarding and a positive Murphy's sign. The haemoglobin was 9.6 g/dl, white cell count $9.6 \times 10^9/1$ and the plasma urea and electrolytes were within normal limits. A pro-

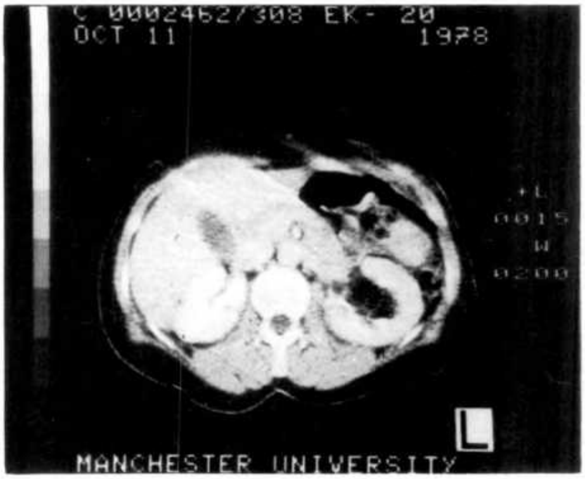

Fig. 1 CT scan of case 1, demonstrating central mass of left kidney.

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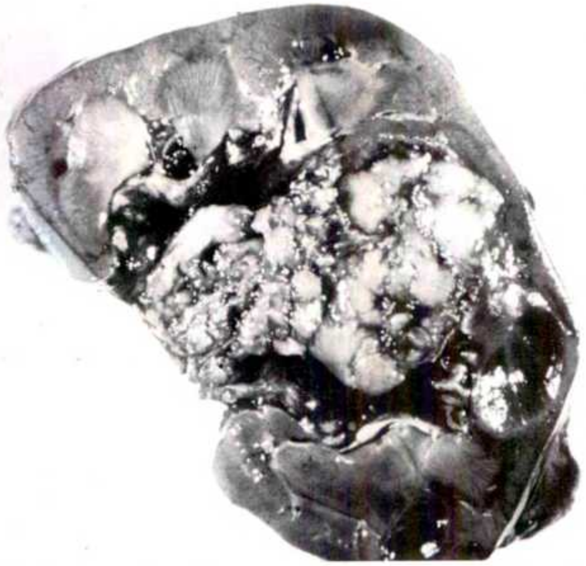

Fig. 2 Bisected kidney of case 1, demonstrating central angiomyolipoma.

visional diagnosis of acute cholecystitis was made and she was treated with analgesics, antibiotics and intravenous infusion. As there was no improvement in the clinical state in the following 3 days and as the haemoglobin fell to 8.4 g/dl, a laparotomy through an upper paramedian incision was performed. This revealed blood-stained peritoneal fluid and the liver, which felt spongy, was found to occupy the whole of the right side of the abdomen. There was enlargement of the right kidney which felt cystic. The gall bladder and other abdominal organs were normal. A liver biopsy was performed and the abdomen was closed. Post-operatively she continued to suffer from right loin pain, although it was less severe. Further investigations were undertaken. An IVU showed a large space-occupying lesion in the upper pole of the right kidney. Ultrasound appearances were those of a complex lesion in the upper posterior abdomen. Angiograms showed some venous pooling but did not show any abnormal circulation or vessels to suggest a neoplasm. A CT scan demonstrated a solid mass in the right kidney with areas of low attenuation values within it. The kidney was explored through a thoraco-abdominal incision and was found to have a large cystic tumour in the upper pole. This "cyst" was opened and found to contain a blood clot and a large amount of necrotic yellow material. A nephrectomy was then performed. The histological picture was similar to that of the first case and was characteristic of angiomyolipoma.

Neither patient had signs or other stigmata of tuberous sclerosis. Both of them are well at the time of writing 11 and 6 months following nephrectomy.

Discussion

Angiomyolipoma is an uncommon tumour of the kidney. Hadju and Foote in a histopathological study of 8501 renal tumours found only 27 cases of angiomyolipoma (Barrilero, 1977). There are 3 varieties of this lesion. They are:

1. Asymptomatic angiomyolipoma of the kidney associated with tuberous sclerosis.
2. Tumours discovered incidentally at autopsy.
3. Symptomatic tumours not associated with tuberous sclerosis.

Between 50 and 80% of patients with tuberous sclerosis have renal angiomyolipomas which are often asymptomatic, small, bilateral and multiple (Deeths and Melson, 1975; Busch *et al.*, 1976; Walker *et al.*, 1976; Mouded *et al.*, 1978). Similar tumours may be found in the brain or the heart.

In patients without tuberous sclerosis the tumours are usually single and cause symptoms. They are 4 times more common in females (Walker *et al.*, 1976; Mouded *et al.*, 1978). They commonly present with symptoms of loin pain, a mass in the loin, shock due to haemorrhage and haematuria. Symptoms of cystitis, contralateral loin pain and hypertension have also been reported (Walker *et al.*, 1976; Barrilero, 1977; Mouded *et al.*, 1978), though it is possible that these symptoms may necessitate urological investigations and the tumour is found incidentally. The pain is thought to be due to repeated small haemorrhages into the tumour (Deeths and Melson, 1975). Case 2 in the present series presented with severe right-sided abdominal pain which was probably due to bleeding into the tumour.

An accurate pre-operative diagnosis of angiomyolipoma is often difficult and it may not be possible to differentiate from an adenocarcinoma. Radiological investigation may help and a number of diagnostic features have been described.

On the plain X-ray film of the abdomen, radiolucent areas may be seen in the region of the tumour and this sign is said to be pathognomonic (Baron *et al.*, 1977). This is due to the high fat content of the tumour which allows only a low absorption of the radiation (Mouded *et al.*, 1978). The detection of these radiolucent areas can be improved if tomograms are performed before the injection of the intravenous contrast (Baron *et al.*, 1977). It is nevertheless difficult to make a firm diagnosis on this sign alone, since it may be present in only 9% (Walker *et al.*, 1976) and may be seen only when the films are looked at retrospectively (Barrilero, 1977). Certainly Baron *et al.* (1977) appreciated this sign only on retrospective inspection of the plain films. Furthermore, bleeding into the tumour will abolish this sign (Deeths and Melson, 1975; Mouded *et al.*, 1978). Some authors have stressed that calcification within the tumour is an important feature of angiomyolipoma (Deeths and Melson, 1975). However, Walker *et al.* (1976) reported that this was present in only 6%. In addition, calcification is not a feature unique to angiomyolipomas. Daniel *et al.* (1972), in a review of 2709 renal masses, found radiologically detectable calcification in 1 to 2% of renal cysts and 10% of adenocarcinomas.

The appearances on intravenous urography are of a space-occupying lesion in the kidney with elongation and compression of the calices (Walker *et al.*, 1976; Barrilero, 1977). These are not specific for angiomyolipoma and are impossible to differentiate from carcinoma (Mouded *et al.*, 1978).

Ultrasound examination in our 2 patients failed to differentiate the lesions from adenocarcinoma. Although reports on the value of this investigation in the diagnosis of angiomyolipoma are limited, Walker *et al.* (1976) considered that a solid lesion with numerous internal echoes was suggestive of angiomyolipoma.

CT as a diagnostic tool has only recently become available and its role in the investigation of renal masses is being evaluated. Certainly in our first case the CT report was confident in diagnosing a tumour consisting predominantly of fat. CT of the kidney in the second case showed areas of low attenuation within the tumour but a diagnosis of angiomyolipoma was not made.

It appears that the presence of the fat in the tumour is more readily detected by CT because of its unique sensitivity in detecting differences in attenuation of X-rays by different tissues. The presence of fat is suggested by characteristically low attenuation values. However, the interpretation of the scan may be confused if there has been a recent haemorrhage into the tumour altering the attenuation.

Angiography may be useful. The classical features described are the presence of aneurysmal dilatation of interlobular arteries and tortuous corkscrew-like vessels (Baron *et al.*, 1977; Barrilero, 1978). These may not be constant, as shown in our second case.

Macroscopically these tumours are yellow and resemble fat and there may be evidence of haemorrhage into the tumour. Microscopically, angiomyolipoma is composed of fat, smooth muscle and blood vessels in varying proportions. The fat tissue is formed by mature adipose cells, but sometimes large hyperchromatic nuclei with bizarre appearances may be seen. The blood vessels are tortuous and have characteristically eccentric lumina with a reduced amount of elastic tissue, and these factors may be responsible for their tendency to rupture (Mouded *et al.*, 1978). There are a few isolated reports of the tumour extending into the renal vein. Angiomyolipoma may be multicentric in both the kidney and its regional lymph nodes, thereby mimicking a malignant tumour with secondaries (Busch *et al.*, 1976) and may extend into the renal pelvis (Cass and Ireland, 1972; Colabawalla, 1972). In our first case the tumour was found extending into the pelvis of the kidney.

The treatment recommended for these tumours is controversial. No one has denied the benign nature of these lesions but opinion regarding their management is divided.

Conservative procedures such as open renal biopsy, wedge resection, partial nephrectomy and no intervention at all have all been recommended (Walker *et al.*, 1976; Barrilero, 1977). Others advocate nephrectomy as a definitive treatment (Colabawalla, 1972; Mouded *et al.*, 1978).

The arguments in favour of the more aggressive approach to the tumour are as follows:

1. These tumours are extremely difficult to diagnose pre-operatively and one can never be sure even during the operation that it is not an adenocarcinoma.

   For example, Walker *et al.* (1976) made a pre-operative diagnosis of renal angiomyolipoma in only one of their 4 cases and Barrilero (1977) in 3 out of 10 patients, and a partial nephrectomy was performed in all of these cases. Mouded *et al.* (1978) suspected angiomyolipoma in 2 of their 8 cases pre-operatively but nephrectomy was performed because of highly suspicious appearances at the operation.
2. Even when an accurate diagnosis is possible, if left alone angiomyolipoma may cause serious complications, including life-threatening haemorrhage due to rupture of blood vessels and damage to the renal tissue by progressive expansion and compression.
3. Angiomyolipoma may have a multicentric

origin within the same kidney (Cass and Ireland, 1972) and if there is a small tumour in the part of the kidney remaining after a partial nephrectomy, this may expand later and require a further operation.

4. Though extremely rare, there may be sarcomatous elements within the tumour.

In conclusion, we feel that renal angiomyolipomas are not just diagnostic curiosities but pose several problems in management. While they are benign in the sense that they do not infiltrate or metastasise, they have a tendency to produce haemorrhage and functional impairment of the kidney by expansion and compression. In view of the difficulty in accurate diagnosis of these tumours pre-operatively it is essential that the kidney should be explored. If pre-operative or per-operative suspicions are high, a frozen section biopsy may be of some help and, if the diagnosis is certain, conservative surgery may be attempted, bearing in mind that there is a possibility of missing another lesion in the remaining parenchyma. It is, however, extremely difficult to do this if the tumour is centrally located. In such cases, and in cases where the diagnosis is uncertain, the treatment of choice is a nephrectomy, assuming of course that the contralateral kidney is normal.

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Chemical Test of Phosphates in Urinary Stones by Means of the Chromographic Contact Print Method

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Summary—The chromographic contact print method, making use of the ammonium phosphomolybdate-ascorbic acid reaction, is used to detect phosphates and to view their distribution in urinary stones. This sensitive reaction may take place even if phosphates, especially apatite, are present in such small amounts as to be under the confirmation limits of microscopic observation, and X-ray and infrared analyses.

The chromographic contact print method, which will be referred to as the print method, is a form of qualitative chemical analysis which has been used in the fields of metallurgy, chemistry, and metallic ore mineralogy (Williams and Nakhla, 1951).

A gelatine-coated paper is impregnated with an appropriate attacking reagent, nitric acid being used in the present method. On pressing the polished surface of a sample against the gelatine side of the paper, the susceptible minerals are attacked and the liberated ions become trapped in the gelatine film. After the paper is removed it is developed in a reagent that is specific for the ions. A coloured print then appears and shows the distribution of the ions throughout the polished surface.

This study is concerned with the chemical analysis of phosphates in urinary stones using the print method.

Material and Methods

Each test sample is cut into 2 parts. The cut-plane is made to cross the central area. One piece is used for the print method and successively for making a thin section to be observed under the polarising microscope, and the other piece is subjected to X-ray, infrared and other analyses.

The powder sample used for X-ray diffraction is obtained by pulverising the whole of the cut surface on a file and the powder samples which are taken by scratching several different parts in the cut surface with a needle are analysed respectively by infrared spectrometry.

The cut surface used for the print method is ground and polished on a plate glass using waterproof sandpaper.

A gelatine-coated paper used for the print method is prepared by thoroughly dissolving and removing the silver salts from an ordinary photographic printing paper.

Reagents are Prepared as Follows:

1. Ammonium molybdate solution: 5 g ammonium molybdate are dissolved in 100 ml distilled water and 35 ml concentrated nitric acid are added.
2. Ascorbic acid solution: 100 mg L-ascorbic acid are dissolved in 100 ml distilled water.

The gelatine film on the paper, cut to an appropriate size, is impregnated with the ammonium molybdate solution and the excess removed by applying dry filter paper. The stone is then laid with the polished surface downwards on the gelatine film and pressed with a handpress for 1 to 4 min. A pressure of 0.5 kg/cm^2 on the polished surface of the stone is required. A piece of plasticine may be placed on the stone before printing. When the reaction paper is peeled off, a yellow print is obtained. After it is dried in room air, a filter paper moistened with the ascorbic acid solution is placed on it and pressed gently for several seconds. When the filter paper is removed, the partial change in colouration is observed on the gelatine film. This operation is repeated several times until the yellow colouration has changed completely to blue. The areas of phosphate on the polished surface are then printed more clearly

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as the blue areas on the gelatine film than as the original yellow areas. The print method can be used repeatedly on newly polished cut surfaces.

The mechanism of the reaction is as follows. The yellow colouration results from the formation of ammonium phosphomolybdate. The blue colouration results from the reduction product of ammonium phosphomolybdate, "molybdenum blue" (Feigl, 1946).

Results

In order to examine the validity of the print method, the test samples were subjected to X-ray diffraction, infrared spectrometry and microscopic observation, and the printed figures were examined closely, comparing them with the results obtained from the above studies.

Thirty stones were studied. Their mineral compositions, determined by X-ray and infrared analyses, are shown in the Table.

The results obtained from 30 printed figures are as follows:

Table Mineral compositions and locations of urinary calculi studied

Mineral composition	*Location*	
	Upper urinary tract calculi	*Lower urinary tract calculi*
Whewellite and apatite	8	0
Whewellite, weddellite and apatite	4	4
Whewellite, uric acid and apatite	2	1
Whewellite, weddellite, uric acid and apatite	1	1
Struvite and apatite	2	1
Struvite, newberyite and apatite	1	0
Struvite, newberyite, weddellite and apatite	0	1
Uric acid and apatite	0	1
Cystine and apatite	1	0
Ammonium acid urate, whewellite, weddellite and apatite	1	0
Brushite, whewellite, weddellite and apatite	1	0
Total	21	9

Whewellite: calcium oxalate monohydrate.
Weddellite: calcium oxalate dihydrate.
Struvite: magnesium ammonium phosphate hexahydrate.
Newberyite: magnesium hydrogen phosphate trihydrate.
Brushite: calcium hydrogen phosphate dihydrate.
Apatite: hydroxyapatite or carbonate-apatite.

(1) The outline of the cut surface was clearly delineated on a printing paper in all but one case. Apatite was commonly detected at the surface. The blue colouration along the outline was usually quite strong and not proportional to the amount of apatite found at the surface.

(2) Urinary calculi often have pores of various sizes. Pores were prominent in the area consisting of a mixture of randomly orientated crystals of whewellite and fine grained apatite. Most of the pores observed on the polished surface were easily recognised on the printed figure as deep blue flecks which usually corresponded to a relatively small amount of apatite found at the walls of the pores.

(3) The blue areas other than pores or cracks were shown in all printed figures and corresponded to the areas of phosphate on the polished surface. Similar blue colourations were observed in response to such phosphates as apatite, struvite, newberyite and brushite. Other phosphates were not found in the 30 test samples. It is usually impossible to distinguish between these phosphates on the printed figure. Fine grains of apatite may be attacked more easily than large crystals of struvite, showing stronger colouration than the latter.

(4) The areas showing well-developed radial striation composed of whewellite or uric acid did not show the blue colouration.

(5) Although oxalates interfere with the formation of ammonium phosphomolybdate, a trace of apatite contained in the area composed mainly of calcium oxalate could be detected by the print method, showing light blue colouration on a printing paper. This colouration may be compared with the deep blue colouration corresponding to a trace of apatite contained in the area composed mainly of uric acid or cystine.

It is considered that the print method is especially useful in detecting phosphate in the areas of uric acid or cystine.

Detailed descriptions of the 7 printed figures are as follows:

Example 1 (Vesical Stone)

This stone is composed of apatite, whewellite and weddellite. The fluffy materials in the central pore, consisting of apatite and whewellite, have been lost in grinding the cut surface. The central pore is surrounded by concentric layers which consist of apatite layers alternating with whewellite layers or weddellite layers at the surface. The

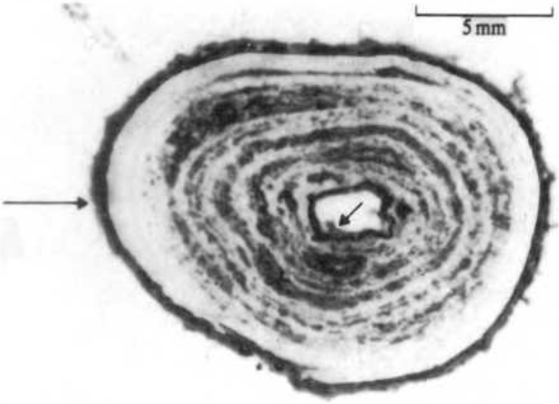

Fig. 1 Chemical print: the outline of the cut surface is blurred exteriorly and that of the pore interiorly (arrows).

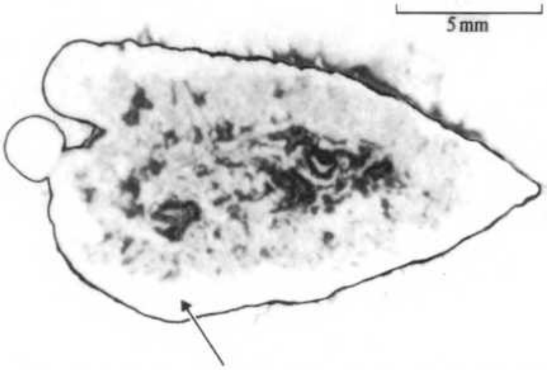

Fig. 3 Chemical print: arrow indicates the thin colourless zone surrounding the blue coloured core area.

apatite corresponds to the deep blue layers and the oxalate, invariably accompanied by a small amount of apatite, to light blue layers on the printed figure (Fig. 1). The outline of the cut surface is blurred outward and that of the pore inward.

Example 2 (Right Renal Stone)

The porous core area consists of a mixture of randomly orientated crystals of whewellite and fine grained apatite. The core area is surrounded by a radially striated layer of whewellite. This layer is divided into 2 parts by a thin layer of apatite which is well demonstrated as an irregular blue band on the printed figure (Fig. 2).

Example 3 (Right Renal Stone)

The porous core area consists of a mixture of randomly orientated crystals of whewellite and fine grained apatite. The outer thin layer, showing well developed radial striations and composed of whewellite, is observed as the colourless zone surrounding the blue core area on the chemical print. Strong blue flecks in the core area correspond to small pores (Fig. 3).

Example 4 (Vesical Stone)

Large crystals of struvite accompanied by a small amount of newberyite occupy the core area, showing a light blue colouration. The deep blue layers surrounding the core area correspond to the alternating concentric layers of apatite and struvite. A thin layer of weddellite observed at the surface is shown as the narrow colourless zone on the printed figure (Fig. 4).

Example 5 (Vesical Stone)

The presence of phosphate could not be confirmed by X-ray and infrared analyses or microscopic observation, which proved the presence only of whewellite and uric acid. The former, showing a well developed radial striation, is present at the

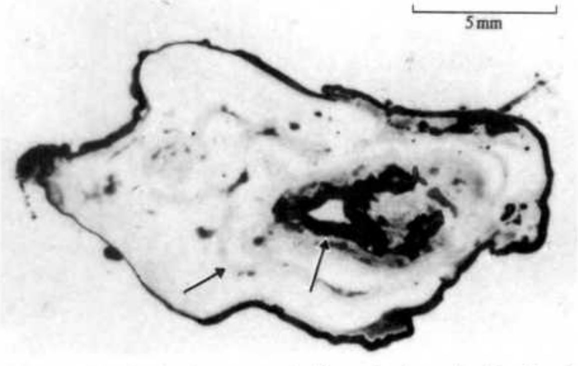

Fig. 2 Chemical print: arrows indicate the irregular blue band and the margin of a large pore in the core area.

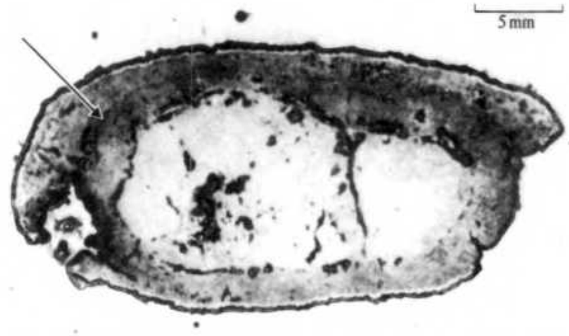

Fig. 4 Chemical print: arrow indicates deep blue layers, where the spaces between struvite layers are occupied by fine grains of apatite.

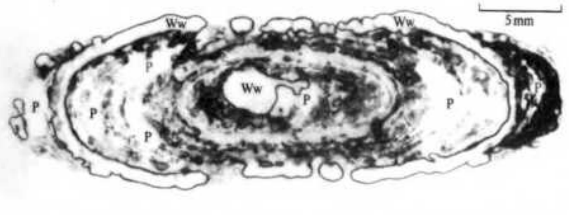

Fig. 5 Chemical print: "P" indicates pores and "Ww" indicates the area of whewellite.

core area and in the surrounding thick layer composed of the latter. Unexpectedly, the blue colouration occurred in the whole area of uric acid. The area of whewellite is shown as the colourless zones demarcated by the distinct blue line (Fig. 5).

Part of this stone was pulverised on an agate mortar, heated at 500 to 600°C for half an hour and then analysed by X-ray. Uric acid, the principal constituent in this stone, was decomposed entirely by this procedure. Apatite peaks then became discernible together with the peaks from the ignited products of whewellite such as $CaCO_3$, CaO and $Ca(OH)_2$ on the X-ray chart of the white residue obtained.

Example 6 (Right Renal Stone)

There is a large pore at the core area of this stone, surrounded by concentric layers which are divided into the interior zone, composed of uric acid, and the exterior zone, composed of whewellite. Although no other constituents were detected by X-ray and infrared analyses and microscopic observation, the blue colouration was observed around the central pore in the interior zone, along the boundary between the 2 zones, and along the outline (Fig. 6).

Electron X-ray microanalysis of the interior zone also failed to detect phosphorus. Then the powder taken from the interior zone was heated to 650°C at a rate of 10°C per min and the ignited product was subjected to infrared analysis. The chart of infrared analysis demonstrated the presence of apatite. It is considered that the blue colouration observed along both the boundary and the outline may also be due to the presence of a trace of apatite.

Example 7 (Left Renal Stone)

This stone is composed of cystine and apatite. The presence of apatite, suspected by X-ray analysis, was confirmed by infrared analysis of the ignited product. The distribution of apatite is clearly depicted on a printing paper (Fig. 7).

Discussion

The study of the texture and composition of urinary stones may provide a new approach to the management of urolithiasis. Study of the texture is especially useful in order to know the environmental conditions which influence the formation of urinary calculi.

Phosphates are significant constituents of calculi and apatite is the commonest of these. Apatite in urinary calculi is usually seen as aggregates of fine grains under the microscope, and the aggregates appear to be optically isotropic because of its low birefringence. Consequently, apatite is apt to be overlooked or confused with some organic materials under the microscope. It is also difficult to detect a small amount of apatite present as a minor constituent by X-ray analysis because of its lower crystallinity, and by infrared analysis

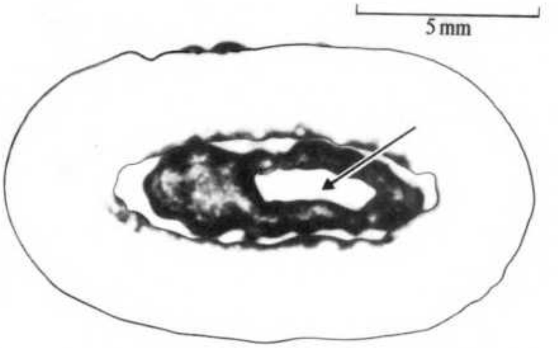

Fig. 6 Chemical print: arrow indicates the central pore. Blurring at the margins is negligible.

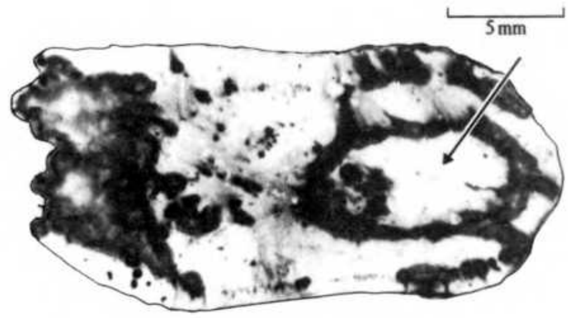

Fig. 7 Chemical print: arrow indicates the core area. Neither pores nor cracks are found on the cut surface.

especially when associated with uric acid or cystine.

The finding of phosphate on the printed figure where not found by the above techniques may indicate the high sensitivity of the colour reaction. In order to confirm this the powder sample taken from the area in question, composed mainly of uric acid, cystine or ammonium acid urate, was ignited and the residue studied by X-ray or infrared analysis, which showed the presence of apatite in these areas.

The ammonium molybdate solution may accumulate at the margins of cut surfaces and pores on printing, resulting in the formation of more ammonium phosphomolybdate than is expected. This is why the strong blue colouration is observed at these margins. In some test samples the distinct blue coloured outline was obtained, though phosphates were not detected at these surfaces by means of X-ray and infrared analyses. It is considered that this colouration may still be due to the presence of a trace of apatite at these surfaces.

Our study may indicate that apatite is contained in almost all calculi and is commonly present at the surface of calculi and at the walls of pores; phosphates derived from urine or blood can be discounted, since the cut surface is ground and polished sufficiently in running water. The print method, with the aid of X-ray, infrared or other means, is effective in revealing the distribution of apatite in urinary calculi.

The following points should be noted:

(1) Ammonium molybdate is also affected by ascorbic acid, with the appearance of light blue colouration. This colouration tends to fade away rapidly and is barely seen in the areas of calcium oxalate because oxalates form stable complex compounds with molybdenum (Feigl, 1946). Therefore it rarely interferes with the interpretation of the typical blue colouration. However, an excess of reagents added to the gelatine film should be avoided.

(2) It is difficult to obtain a clear-cut print by the print method because of diffusion of the reaction products. This is prominent at the margins of cut surface and pores. The outline of the cut surface tends to be blurred exteriorly and that of the pores interiorly, so that small pores are often seen as deep blue flecks on a printing paper. To prevent diffusion, the reaction paper removed from the polished surface should be dried almost completely and the ascorbic acid solution should be added gradually.

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Carcinoma of the Bladder Treated by Interstitial Irradiation

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Summary—A retrospective study is presented of 180 patients with clinically infiltrating transitional cell carcinoma of the bladder treated by interstitial irradiation. The cases were re-classified by clinical tumour extent and histopathological grade according to the UICC (1978) classification. The actuarial survival rates and complications are presented and treatment policy reviewed.

There has been a resurgence of interest in interstitial irradiation of the bladder for certain circumscribed tumours (Werf-Messing, 1978). Although several types of radioactive sources are suitable for this purpose (Dix *et al.*, 1970; Bloom and Wallace, 1971), the principal materials used are gold^{198} grains and tantalum^{182} wire.

Although carcinoma of the bladder is a manifestation of a generalised urothelial disease, a conservative local approach to the condition is worthy of consideration, since alternative treatment such as megavoltage therapy or cystectomy can follow interstitial irradiation, if the latter fails.

The cases suitable for interstitial irradiation are highly selected, being restricted to patients with T1 or T2 tumours which are solitary, not greater than 4 cm in diameter, of minimal de-differentiation and with limited invasion. As these are essentially clinical staging criteria, it is important to review previous experience and see how accurately these criteria were achieved and with what success in relation to prognosis.

Patients

Between 1958 and 1976, 180 patients were treated at The Royal Marsden Hospital for transitional cell carcinoma of the bladder by interstitial irradiation using either gold^{198} grains or tantalum^{182} wire pins. Thirty-three patients were excluded because they could not be staged clinically (TX—16 cases), or pathologically (pTX—17 cases).

Of the remaining 147 patients, one of us (P.A.T.) has reclassified their tumours according to the UICC (1978) system, with attention to cellular differentiation (G1-G3), bladder wall invasion and the presence of carcinoma *in situ* (Table 1). Forty-three of the 47 tumours (91%) classified in the T1 category were confirmed to be pT1. Of the 76 patients in category T2, 30 had no evidence of muscle invasion on *biopsy* (*i.e.* in only 60% was the depth of infiltration substantiated). Twenty-two of the 24 T3 cases had histological evidence of deep muscle invasion (91%). There was therefore considerable difficulty in determining accurately the clinical category in tumours invading superficial muscle.

Results

The actuarial survival at 5 years according to T category is shown in Table 2: 69% of patients with T1 lesions and 21% of patients with T3 lesions are alive at this time, and many have survived beyond 10 years. If survival according to pT category is considered, then 73% of pTa, 57% of pT1 and 33% of pT2 cases survived 5 years (Table 3). Survival data according to cellular differentiation are remarkably similar to those based on the degree of tumour infiltration (Table 4).

Although much has been written about the presence of concomitant *in situ* carcinoma around the tumour, such mucosal changes did not affect the survival of T1 and T2 cases (Table 5). However, no biopsies were taken from sites distant to the tumour region. Recurrence of bladder cancer after open interstitial irradiation compared with transurethral diathermy appears to be reduced, the latter being necessary at a later date in only

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Table 1 Comparison of Clinical T and Biopsy Stage by Histological Grade

	TA/T1			*T2*			*T3*		
	pTa	*pT1*	*≥pT2**	*pTa*	*pT1*	*≥pT2**	*pTa*	*pT1*	*≥pT2**
G1	22	1	0	0	0	1	0	0	1
G2	10	7	2	2	17	14	0	0	5
G	0	3	2	0	11	31	0	2	16
Total	32	11	4	2	28	46	0	2	22

* It is often impossible to be precise about the depth of muscle invasion on biopsy or reamings.

Table 2 Clinical Stage and Actuarial Survival

	Total cases	*Alive 5 years*	*n*	*Alive 10 years*
T1	47	69%	28	40%
T2	76	41%	39	21%
T3	24	21%	4	11%
Total	147	46%	71	25%

n = Number of patients alive at 5 years and valid for assessment at 10 years.

19% of T1 lesions and in 16% of T2 lesions. Other recurrences were more serious, requiring total cystectomy in 7% of all cases (Table 6).

Interstitial irradiation carries a low morbidity and mortality rate (Table 7): the post-operative death rate was only 1.4%. However, vesicoureteric reflux was found in 25%. This had been previously noted (Williams *et al.*, 1971), but we now have a much longer follow-up: 3 of 36 refluxing patients had persistent infected urine and proceeded to pyelonephritic scarring and hypertension.

In choosing the type of implant, gold^{198} has the advantages that it is easily applied and does not have to be removed. Although the radiation dose (in rads) was comparable for both gold^{198} and tantalum^{182}, the 5-year results appear to be different for T1 and T2 cases (Table 8). It is possible that the more accurate application and more uniform irradiation associated with the tantalum^{182} sources are responsible for the lower recurrence rate. On the other hand, gold^{198} grains are more adaptable to a volume implant for the thicker type of T3 lesion and this may account for the greater survival rate associated with this isotope compared with tantalum^{182}.

Table 9 depicts the influence of age on death from carcinoma of the bladder; other causes of death have been removed from this chart. Fifteen patients died from double primary tumours and 33 patients died of respiratory or cardiovascular causes and not of carcinoma of the bladder.

Discussion

The results in this study have shown that the criteria for interstitial irradiation cannot always be made on purely clinical grounds and must be supplemented by histological data obtained from biopsy material in accord with the UICC (1978) classification. The results with interstitial irradiation for T1 tumours are similar to those following transurethral resection (Whitmore, 1979) and, as a general rule, we recommend the latter for initial treatment of such lesions. However, the recurrence rate in patients with non-infiltrating tumours treated by radio-implant is unusually low (Table 6). In such cases, and even in those with T2 tumours, the presence of *in situ* change

Table 3 Actuarial Survival of T1 and T2 Patients According to Extent of Histological Invasion

	Total cases	*Alive 5 years*	*n*	*Alive 10 years*
pTa	34	73%	21	45%
pT1	39	57%	16	29%
pT2	50	33%	13	15%

n = Number of patients alive at 5 years and valid for assessment at 10 years.

Table 4 Actuarial Survival of T1 and T2 Patients According to Histological Grade

	Total cases	*Alive 5 years*	*n*	*Alive 10 years*
G1	24	78%	14	50%
G2	52	53%	21	25%
G3	47	37%	15	20%

n = Number of patients alive at 5 years and valid for assessment at 10 years.

Table 5 Flat Carcinoma *in situ*: Influence on 5-year Actuarial Survival (G2/G3 cases only)

	Total cases	*Tis negative*	*Total cases*	*Tis positive*
T1 (G1)	23	82%	—	—
T1 (G2/G3)	15	65%	9	56%
T2 (G1)	1	100%	—	—
T2 (G2/G3)	59	39%	16	48%
Total G1	24	83%	—	—
Total G1/G3	74	44%	25	50%

in the adjacent mucosa did not appear to increase the recurrence rate or reduce survival. It is possible that the local irradiation of any surrounding *in situ* tumour by the radio-implant inhibits further proliferation of the abnormal epithelium. Furthermore, there were no instances of pulmonary metastases in patients with non-infiltrating tumours after radio-implant, whereas this serious complication is well documented following transurethral resection. Thus, for recurrent solitary T1 tumours, especially of G2 or G3 malignancy, we would consider further treatment by interstitial irradiation.

In carefully selected T2 cases, even with G2 or G3 lesions, interstitial irradiation gives results which appear to be comparable to those obtained by more radical procedures such as whole bladder irradiation, cystectomy or a combination of preoperative irradiation and cystectomy. The 5-year survival rate of 24% for patients with T3 tumours treated by implantation of radio-gold seeds (Table 8) is not inferior to that following radical cystectomy and comparable to various series treated by external beam therapy (Bloom, 1980). These cases, of course, are selected in having tumours of limited diameter suitable for an implant. However, in view of their deep infiltration and frequent association with lymph node metastases, we regard T3 lesions as generally constituting a "pelvic" malignancy and therefore unsuitable for local radiotherapy: such tumours are better managed by regional treatment such as provided by external beam irradiation alone or in combination with cystectomy.

Table 6

	Original stage		
	T1 (47)	*T2 (76)*	*T3 (24)*
Recurrences	16	23	7
Close cystodiathermy	9	12	3
External beam radiotherapy	0	8	3
Cystectomy	7	3	1

Table 7 Complications of Treatment

	T1 (n=47)	*T2 (n=76)*	*T3 (n=24)*	*Total (n=147)*
Operative death	0	2	0	2 (1.4%)
Suprapubic urinary leak	2	6	4	12 (8.2%)
Ureteric reflux	5	23	8	36 (25.0%)
Scar implant	0	2	1	3 (2.0%)

We accept that it is often difficult to assess the depth of infiltration of the tumour base from transurethral specimens as they, hopefully, do not include perivesical fat! Nevertheless, our practice is to proceed to an open implant if the biopsy specimen has relatively normal muscle deep to the superficial infiltration. These patients usually follow the UICC criteria that induration of the bladder is palpable before resection but is not palpable after resection. Even under these conditions mistakes can be made. At open operation there may be evidence of deep infiltration of the bladder wall and this will be confirmed in tissue subsequently taken from the tumour base: there may also be lymphatic involvement. In such circumstances, we may proceed with a modified radioactive implant to give a sub-radical dose of irradiation to the tumour base and supplement this with external beam radiotherapy to a much larger volume of tissue including the regional nodes. This procedure was undertaken in 10% of our T2 lesions (Table 6) and therefore it would appear that a high proportion of T2 bladder tumours are suitable for local interstitial irradiation, thereby avoiding the possible complications associated with external beam therapy such as bladder contracture, haemorrhage from radiation telangiectases and, occasionally, bowel stenosis or ulceration. However, we believe that at least some T2 tumours, especially those of G3 malignancy, are best treated by more extensive procedures as for T3 tumours.

Table 8 Influence of Type of Isotope on 5-year Survival

	No. of cases	*T1*	*No. of cases*	*T2*	*No. of cases*	*T3*
Tantalum^{182}	13	100%	23	55%	6	0%
Gold^{198}	34	58%	53	35%	18	24%

Table 9 Influence of Age on 5-year Survival

	No. of cases	*<60*	*No. of cases*	*60-64*	*No. of cases*	*65-75*	*No. of cases*	*>75*
T1	15	87%	10	60%	13	54%	8	55%
T2	21	52%	16	46%	24	28%	15	33%
T3	10	20%	2	0%	8	38%	4	0%
Total	46	56%	28	47%	45	37%	27	35%
Total (excluding deaths due to causes other than bladder tumour)	45	58%	20	65%	34	48%	20	50%

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Experimental Intra-arterial Infusion of Microencapsulated Mitomycin C into Pelvic Organs

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Summary—Laboratory experience with the use of Mitomycin C encased in ethylcellulose microcapsules as an agent for transcatheter embolisation is described. Microencapsulated Mitomycin C (MMC-m.c.) was infused into the pelvic organs of dogs by arterial catheterisation and the distribution of MMC in plasma and tissue was examined.

MMC levels in the circulating blood of the MMC-m.c. group were significantly lower than those of the non-encapsulated MMC group. The biological potential of MMC was retained for prolonged periods in the pelvic organs after intra-arterial infusion of MMC-m.c. On the other hand, MMC could not be detected in the tissue of the non-encapsulated MMC group 4 h after the infusion.

Transcatheter embolisation of the vessels supplying a malignant tumour has been a useful method in the management of patients with urological cancer. Its main indications are embolisation of renal tumours as pre-operative and palliative measures in inoperable cases and embolisation of hypogastric arteries in life-threatening situations such as chronic bleeding from the bladder and prostatic cancer. The anatomical location of the pelvic organs, with their single blood supply from the paired internal iliac arteries, suggests that arterial embolisation could be an ideal form of treatment for advanced pelvic cancer. Various materials have been used for embolic occlusion of the vessels, including autologous tissue (Reuter and Chaung, 1974), gelatin sponge (Goldstein *et al.*, 1975), metal springs (Gianturco *et al.*, 1975) and ferrosilicone compound (Pontes *et al.*, 1976).

We have used arterial embolisation as a method for carrying a chemotherapeutic agent to a tumour so that the drug can exert its maximum effect on residual viable malignant cells following embolisation.

For this purpose we encased Mitomycin C in ethylcellulose microcapsules for transcatheter infusion (Kato and Nemoto, 1978). The microencapsulated MMC allows sustained release of biologically active MMC *in vitro* and *in vivo* (Kato *et al.*, 1979).

In this study we report the intra-arterial infusion of MMC-m.c. into the pelvic organs of the dog and examine the distribution of MMC in the plasma and pelvic organs.

Materials and Methods

The preparation and properties of MMC-m.c. have been described previously (Kato and Nemoto, 1978). Briefly, MMC-m.c. encapsulated with ethylcellulose formed an irregular particle with a rough surface (Fig. 1). The particle size was 224.6±54.9 μm (mean±SD), so that the capsules were readily infused through a Kifa red catheter

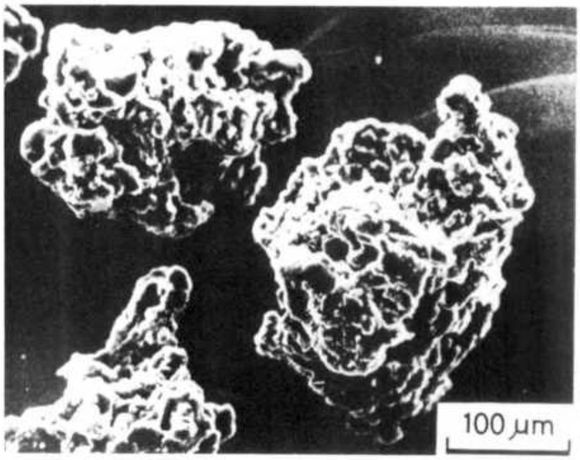

Fig. 1 Scanning electron microscopic finding of microencapsulated MMC with particle size of 224±54.9 μm.

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(1.2 mm in internal diameter). MMC-m.c. consists of 80% (w/w) of biologically active MMC as the core and 20% (w/w) of ethylcellulose as the shell.

A Kifa red catheter was inserted into the common iliac artery of mongrel dogs (weight 10-12 kg) through the right femoral artery. The animals were anaesthetised with intravenous pentobarbital (25 mg/kg). The bilateral external iliac arteries were ligated during the infusion of MMC-m.c. to supply blood to the internal iliac arteries. MMC-m.c. containing 10 mg of MMC was suspended in 60 ml of cold physiological saline and infused into the pelvic organs through the catheter (MMC-m.c. group, 5 dogs). For the controls, 10 mg of non-encapsulated MMC (Mitomycin S, Kyowa Hakko Kogyo Co. Ltd, Tokyo) were infused in the same manner (control group, 3 dogs). The infusion time was 5 min and blood samples were obtained from the right common iliac vein at determined intervals. Extirpation of the pelvic organs, including the rectum, prostate, urinary bladder and lymph nodes around the bilateral common iliac arteries, was done 4 h after the drug infusion. Bioassay for MMC in the serum and tissue homogenate of the pelvic organs was performed by the agar diffusion method using *Esch. coli* B-ATCC 11303.

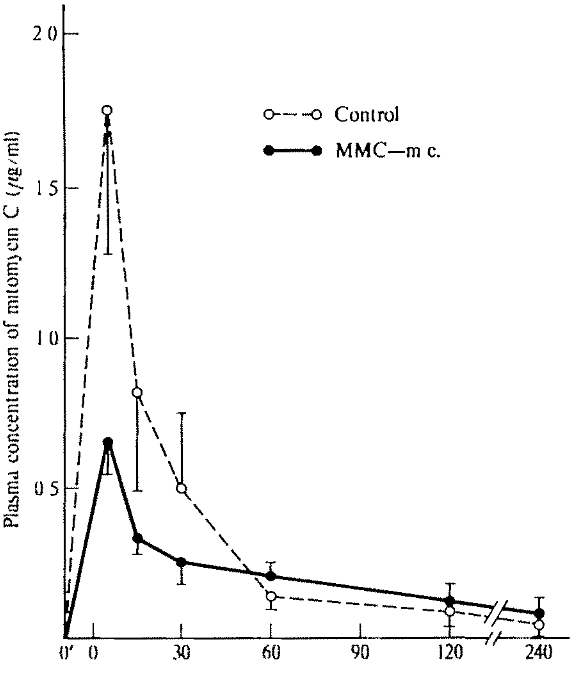

Fig. 2 Plasma levels of MMC after intra-arterial infusion with MMC-m.c. containing 10 mg of MMC and 10 mg of non-encapsulated MMC into internal iliac arteries of dog. 0'-0, infusion time (5 min); bars, mean±SD (n = 5 for MMC-m.c. n = 3 for control). 0-0 MMC-m.c., 0—0 non-encapsulated MMC.

Results and Discussion

MMC levels in the circulating blood of the MMC-m.c. group were significantly lower than those of the control group for 30 min after the intra-arterial infusion ($P<0.01$) (Fig. 2). The highest level of MMC, observed 5 min after infusion, was 0.657 ±0.056 μg/ml (mean±SD, n = 5) in the MMC-m.c. group, while that in the control group (n = 3) was 1.753±0.472 μg/ml ($P<0.005$). The highest level of MMC in the MMC-m.c. group can be attributed largely to dissolution of MMC from the capsules during intra-arterial infusion. In terms of bio-availability, calculated by the area under the blood level curve, the MMC-m.c. group was estimated to release MMC into the cirulating blood by approximately 45% relative to the control group. The reduced bio-availability in the MMC-m.c. group shows that intra-arterial MMC-m.c. produces very low systemic drug levels and prevents unacceptable systemic toxicity as compared with non-encapsulated MMC. Figure 3 shows the distribution of MMC in the MMC-m.c. group (n = 5); mean concentrations of MMC in the prostate, bladder and rectum were 0.129±0.06, 0.127 ± 0.09 and 0.09 ± 0.06 μg/g respectively. Lymph nodes around the common iliac arteries revealed a significant uptake (0.003±0.005 μg/g) of MMC. On the other hand, MMC could not be detected in the tissue homogenates of the control

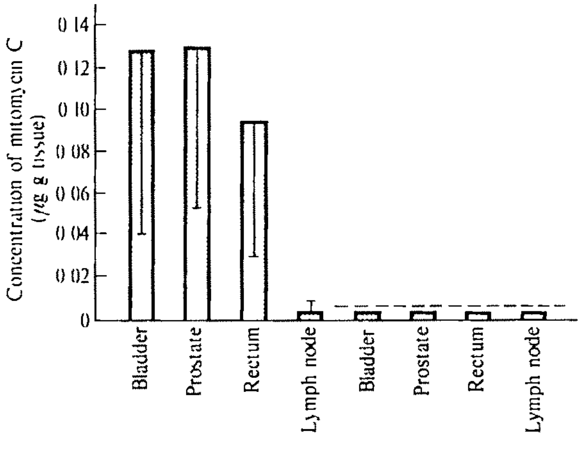

Fig. 3 MMC distribution in pelvic organs of dogs 4 h after intra-arterial infusion with MMC-m.c. and non-encapsulated MMC. Bars: mean±SD. Dotted line: limitation of bioassay.

organs. These findings indicate that MMC-m.c. retains its biological potential for prolonged periods of time in the pelvic organs after arterial infusion of the drug through the internal iliac artery.

These results suggest that if MMC-m.c. were infused into pelvic tumours, intensive topical chemotherapy could be achieved with minimal systemic side effects. In addition, the *in vivo* infusion showed that ethylcellulose microcapsules lodged in the small arteries and reduced the vascularities (Kato *et al.*, 1979). It may be that intra-arterial infusion of MMC-m.c. causes small vessel occlusion in the target site and releases MMC into the surrounding tissue for prolonged periods of time. In other words, transcatheter arterial infusion of microencapsulated MMC into the cancerous organs is a topical regional anticancer chemotherapy together with arterial embolisation of malignant tumour. The clinical application of MMC-m.c. for advanced carcinoma of bladder, prostate and rectum is currently being investigated.

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Genesis of Papillary Tumours: Histological and Microangiographic Study

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Bristol

Summary—The technique developed to study the microangiography of healthy bladders has been applied to study the known vagaries of papillary tumours, their associated changes and their genesis.

Epithelial hyperplasia (reactive hyperplasia), which develops as a form of mucosal self-defence, is a general, non-specific tissue response to an adverse environment. The conversion of reactive hyperplasia into reactive autonomy represents the neoplastic process. The growth of abnormal arteries precedes the development of tumours. A papillary tumour results from a symbiotic growth relationship between such an abnormal artery and the overlying normal or hyperplastic epithelium. All known vagaries of papillary tumours have been studied.

Bladder tumours show 2 major histological patterns—papillary and solid; each behaves differently and has a different prognosis. Papillary tumours, which comprise about 75% of bladder tumours, show certain special characteristics which remain unexplained.

1. They develop more frequently in the neighbourhood of ureteric orifices and the posterolateral walls.
2. They possess branching processes.
3. They may be solitary or multiple, with marked variations in size and shape but with the same histology, or compound—as if 2 or more have coalesced to form one irregular mass.
4. Local removal or diathermy destruction is curative, but tumours with identical histology appear either at the same site or at different sites at irregular intervals.
5. The rest of the bladder epithelium frequently shows either diffuse or focal proliferation, cyst formation, lymphocytic infiltration and, occasionally, metaplasia.

It is felt that the mechanism of genesis of papillary tumours is linked to these phenomena and any explanation thereof, to be credible, should also explain and fit together all of the known characteristics in the form of a jig-saw puzzle.

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Material and Method

This study, which was designed to explain the genesis of papillary tumours, consists of 2 parts: histological and microangiographic.

Histological Study

For the purpose of histology, the operative and biopsy material from an unselected series of 170 patients with papillary tumours of the bladder (treated exclusively by surgery) was studied. The tumour as well as the adjoining mucosa were routinely stained and examined under a light microscope. The tumours were examined for grade and the presence or absence of infiltration. Franksson's grades 1 to 3 were taken as low, 4 and 5 as medium and 6 as high (Franksson, 1950). The smallest tumours were particularly sought after, and the zones of transition between the lining epithelium and the papillary processes were examined. The adjacent mucosa was studied for hyperplasia and defined as follows:

Negative (−) = Complete absence of hyperplasia.
Slight (+) = Uniform hyperplasia about twice the normal thickness or more.
Moderate (+ +) = Focal hyperplasia either with or without uniform hyperplasia.
Marked (+ + +) = Gross bizarre hyperplasia, cystosis or microscopic fronds,

Microangiography

The material for microangiography in neoplastic disease was obtained after total cystectomy had been carried out. It was studied in 10 specimens; in each case the whole of the bladder was sectioned and examined as described by Sarma (1981).

There was, of necessity, some variation in the technique of dissection and preparation of the specimen in the early stages (Sarma, 1981). When possible, the vesical vessels were isolated and divided between ligatures, the ligatures on the side of the bladder being kept long for easy identification. The removed specimen was transferred to a vessel containing normal saline rather than formalin, while the rest of the operation was completed.

The specimen was spread out on a table; the lymph nodes were identified, dissected and placed in separately labelled bottles. A small catheter was introduced through the urethra, the bladder emptied, and about 120 ml of buffered neutral formalin was put in. The rest of the technique of preparation, cannulation, injection, fixation, section and radiography remained as described by Sarma (1981).

The life history of the tumours—grade, recurrences, spread and patients' survival—was studied in the light of epithelial hyperplasia. Microangiographic sections were examined with special reference to (*a*) the general pattern compared with the normal, (*b*) the site/sites where histological abnormalities were identified, and (*c*) bases of tumours. The possible role of the vasculature in the histogenesis of the tumours was assessed and the conclusions were examined in the light of comparative pathology or comparative oncology.

Results

Histological Studies: The Tumour

Of the 170 papillary tumours, 93 were low grade, 68 were medium grade and 9 were high grade as defined by Franksson (1950). Amongst the low grade tumours none was infiltrating, but 11 from the medium grade and 9 from the high grade were infiltrating.

Amongst the non-infiltrating tumours no abnormality of any kind, either histological or cytological, was found in the transitional zones along the bases (Figs. 3 and 4). In small papillary tumours (Fig. 3) the cells forming the tumours were identical in appearance to the cells of the adjoining normal epithelium. As expected, the villi showed connective tissue corium inside which the arteries were prodigious (Fig. 5). Neither regional nor distant metastases were found in the majority. Only 13 of the 20 infiltrating tumours were found to have spread to either the internal or external iliac lymph nodes. Of the total, 4 had metastases in the lungs and they were all medium grade tumours.

All except the 20 infiltrating tumours were treated by local diathermy excision or destruction. Reappearance of the tumour at the same site (after complete clearance had been confirmed by re-examination) was described as recurrence. Tumours occurring elsewhere in the bladder were described as new tumours. Table 1 shows the frequency of local recurrence and Table 2 shows the frequency and nature of the new tumours.

The Adjacent Mucosa

The mucosa away from the tumour showed patchy hyperplasia with occasional cyst formation in 134 out of 170 cases (79%). Closer examination in these areas showed earliest or infant papillary tumours (Figs. 1, 2, 3 and 4). In the remaining 36 cases (21%) there was no epithelial reaction at

Table 1 Result of Local Resection or Destruction with Diathermy

Grade	*Total*		*Recurrence*					
	No.	*%*	*Low*		*Medium*		*High*	
			No.	*%*	*No.*	*%*	*No.*	*%*
Low	93	55	25	27	3	4	0	0
Medium	68	40	4	6	19	28	0	0
High	9	5	Treated by cystectomy					

Table 2 Frequency and Nature of New Tumours Following Local Resection or Destruction with Diathermy.

Grade	*Total*		*New tumours*					
	No.	*%*	*Low*		*Medium*		*High*	
			No.	*%*	*No.*	*%*	*No.*	*%*
Low	93	55	38	41	2	3	0	0
Medium	68	40	18	26	22	32	0	0
High	9	5	Treated by cystectomy					

Note: some recurred more than once.

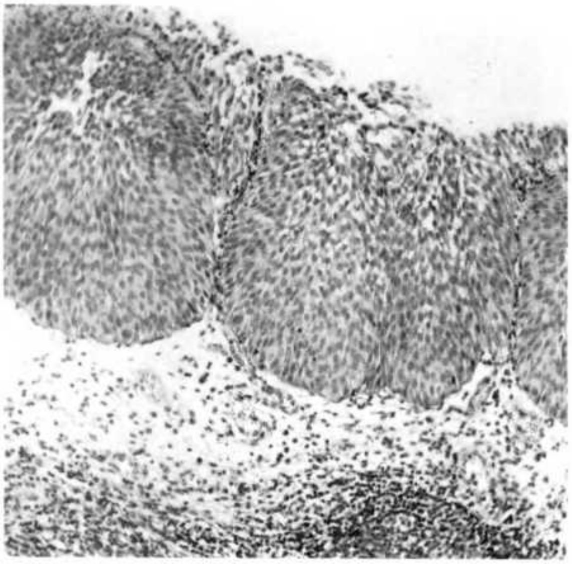

Fig. 1 Focal epithelial proliferation with bladder cancer (+ +) (H and E ×85).

all (*i.e.* negative). Table 3 shows the grade of the tumours seen with various types of hyperplasia. As the hyperplasia progressed from slight to moderate and marked, the grade of the tumours tended to be lower.

Figures 6 and 7 show the frequency of recurrence and new tumours over 5-year and 10-year periods. As expected, the frequency of both recur-

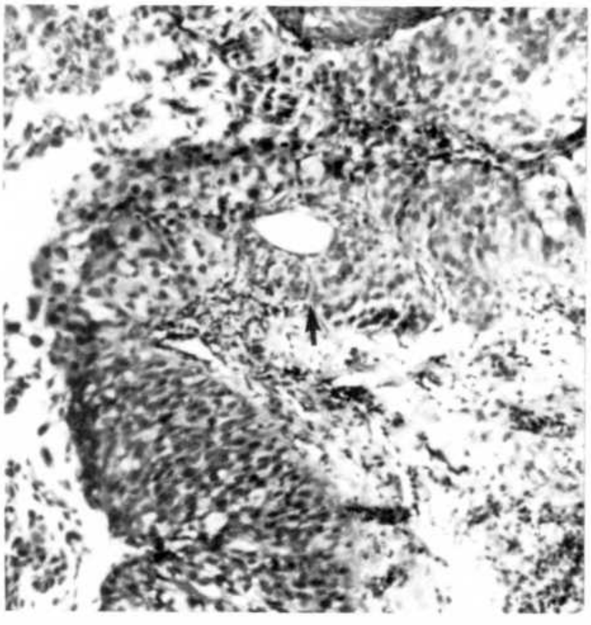

Fig. 2 Focal proliferation with cyst formation (+ + +) (H and E ×195).

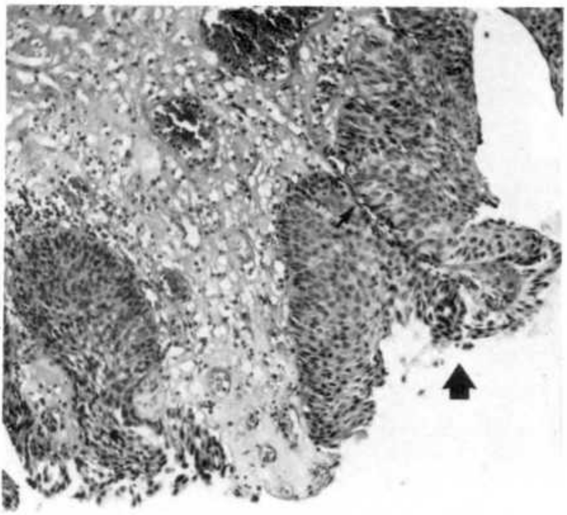

Fig. 3 Focal proliferation with an "infant" papillary tumour. Note the sizeable mucosal artery in the base (H and E ×78).

Table 3 Nature of the Tumours in the Light of Various Types of Epithelial Hyperplasia

Hyperplasia	*Total*		*Tumour grade*					
	No.	*%*	*Low*		*Medium*		*High*	
			No.	*%*	*No.*	*%*	*No.*	*%*
Negative	36	21	16	45	14	39	6	16
Slight	64	38	38	59	24	38	2	3
Moderate	54	32	30	56	24	44	0	0
Marked	16	9	9	56	6	38	1	6

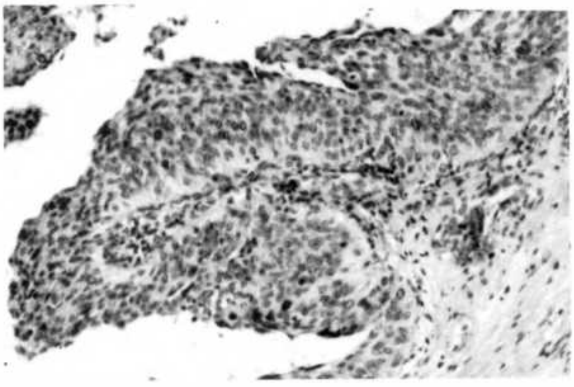

Fig. 4 Further progression of the tumour. Note the large artery in the base (H and E ×101).

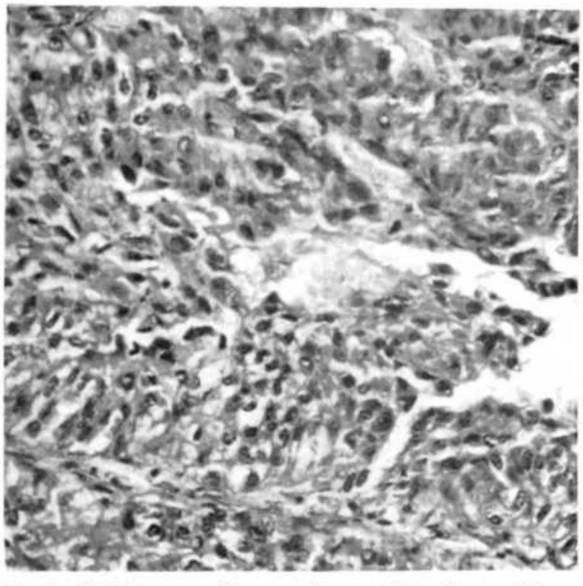

Fig. 5 Full-blown papillary carcinoma. Note the prodigious arterial supply to account for hyperchromasia and mitosis (H and E ×235).

rent and new tumours was greater in a 10-year period, thus stressing the need for prolonged follow-up, but there was no suggestion of any causal relationship between increasing hyperplasia and increasing frequency.

Amongst 13 infiltrating tumours 6 had negative, one had slight, 5 had moderate and one had marked hyperplasia. The 4 tumours with distant metastases all had negative hyperplasia.

Survival

In calculating the survival rate, the 20 patients who had cystectomy and a further 6 who died from unrelated causes were excluded, thus making it easier to study the possible influence of the pathological process. Figure 8 shows the survival rate related to various types of epithelial hyperplasia. As the epithelial hyperplasia increased, both the 2-year and the 10-year survival rates progressively increased.

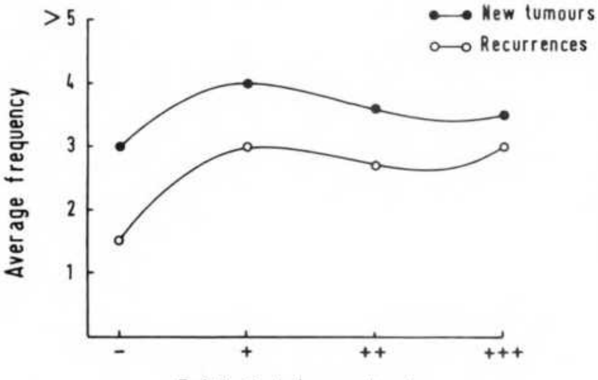

Fig. 6 Frequency of recurrences and new tumours with various types of hyperplasia over a 5-year period.

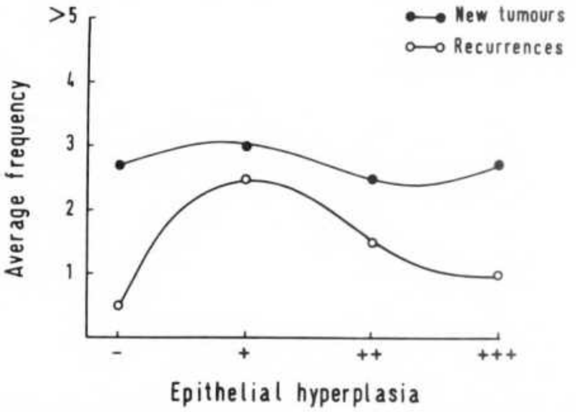

Fig. 7 Frequency of recurrences and new tumours with various types of hyperplasia over a 10-year period.

Microangiographic Studies

Bladders containing papillary tumours showed no general increase in vascularity compared with healthy bladders, and with infiltrating tumours there may even have been a reduction, but abnormal anastomoses giving star-shaped areas were seen on the surface (Fig. 9).

In areas free from tumours, the submucous plexus was the most prominent and the extramural plexus the least prominent. The submucous plexus frequently extended into the mucosa itself

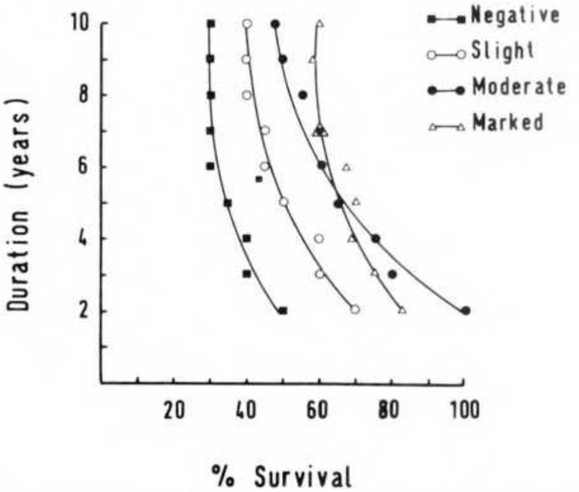

Fig. 8 Survival with various types of epithelial hyperplasia.

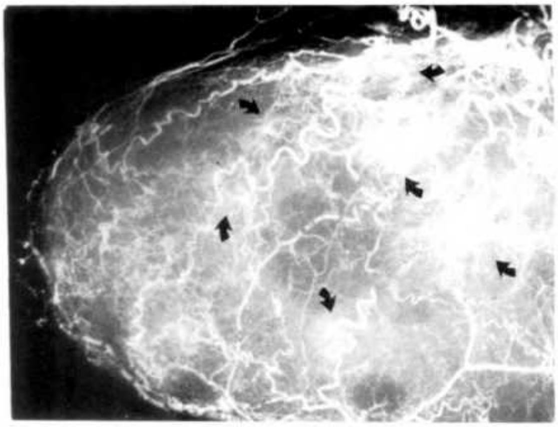

Fig. 9 Angiography of bladder with multiple papillary carcinomas. Note that there is no general increase in vascularity, and also the star-shaped areas of papillary tumours.

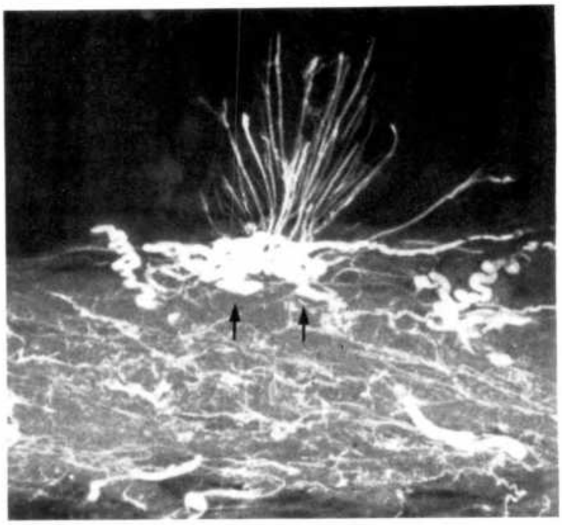

Fig. 11 A small papillary tumour. Note the helicine arteries in the base which straighten within the tumour.

and showed evidence of general arterial and capillary proliferation (Fig. 10). Of special interest were the tortuous vessels, which suggested arterial growth even in the absence of tumours. These helicine arteries could be seen arising from any of the 3 plexuses.

The appearance of the vessels in relation to the base and within the substance of small, medium and large tumours was studied (Figs. 11, 12, 13 and 14). Without exception, they all showed corkscrew-shaped convolutions in the base of the tumours, but within the tumour substance they were straight.

Occasionally a large helicine conducting type of artery was seen to arise from an even larger conducting artery in the submucous plexus and proceed to supply a solitary tumour (Fig. 12). In others, a leash of closely placed helicine conducting type of arteries either from the intramural or from the submucous plexus was seen to supply clearly defined areas (Fig. 13). These were the compound pedunculated tumours. Generally there was no anastomosis within the tumours. In the third variety, 2 or more helicine conducting vessels seemed to form an anastomotic chain in the submucosa, from which leashes of vessels proceeded to supply separate segments of the tumour (Fig. 14). They were broad based and represented the compound sessile type of tumour. Again there was no anastomosis within the tumour itself.

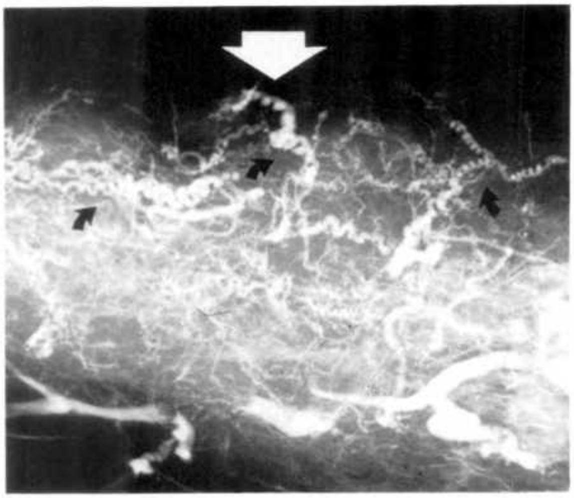

Fig. 10 Microangiography in an area free from tumours, same case as in Figure 9. White marker shows the mucosal surface. Note the helicine mucosal arteries due to primary growth.

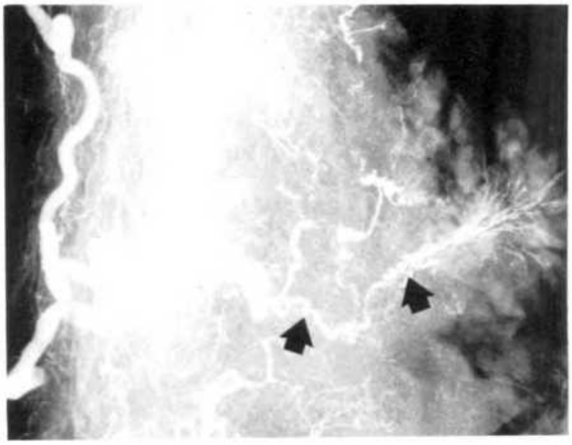

Fig. 12 A solitary papillary tumour and its feeding artery which shows a helicine appearance up to the base of the tumour; within the tumour the branches are straight.

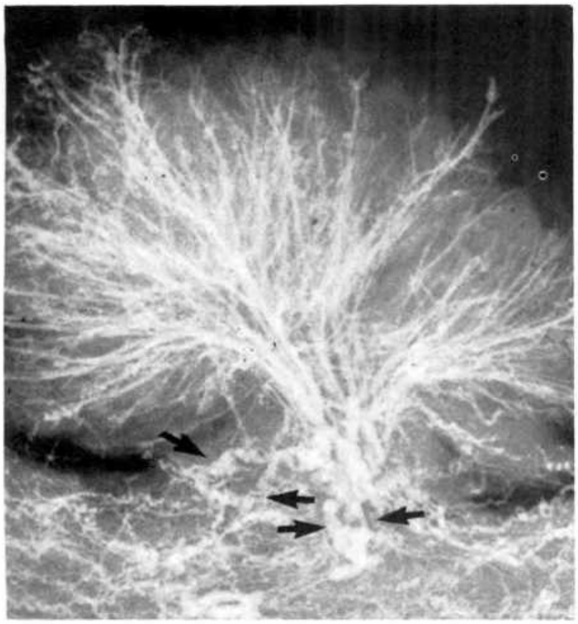

Fig. 13 Same picture of primary arterial growth as in Figure 12 with a compound pedunculated tumour.

Discussion

Development of tumours—whether benign or malignant—is a universal tissue potentiality. Therefore the associated changes in various tissues should be comparable and their significance similar.

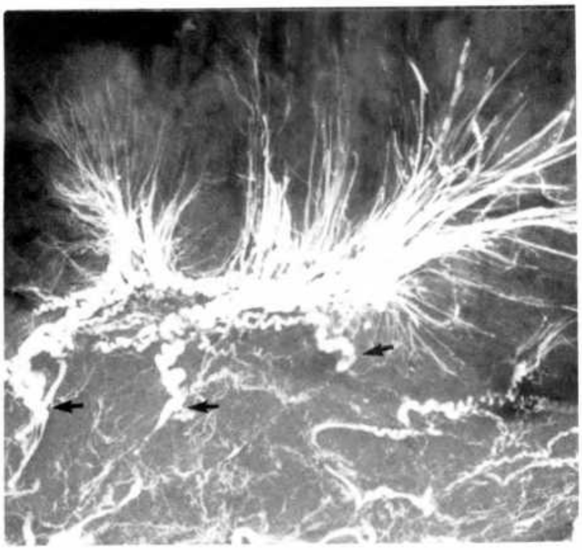

Fig. 14 A compound sessile tumour. Note the coiled arterial chain due to anastomosis between a number of helicine arteries in the submucosa. In the tumour the arteries and the tissue they feed are in equilibrium.

Nature of Epithelial Hyperplasia

Through close and prolonged observation, pathologists have described epithelial hyperplasia as "reactive hyperplasia", particularly when it affects lining membranes. In 79% of papillary bladder tumours there had been some form of epithelial proliferation (hyperplasia). With the urogenous route of carcinogens well recognised (Sarma, 1972) and the entire bladder mucosa thus at risk, it seems strange that in no less than 21% the rest of the mucosa showed no reaction at all. Nor was it apparent why hyperplasia tended to be patchy rather than uniform. This suggests some hitherto unexplained local factors at play.

Table 3 shows that in the absence of hyperplasia all grades of tumours were seen. With slight and moderate hyperplasia (*i.e.* + and ++) high grade tumours were rare, but low and medium grade tumours were common. With the entire bladder mucosa at risk, it is only logical that the epithelial reaction and the associated tumours showed such a pattern in a significant number of cases. Figure 8 shows that with an increase in hyperplasia the survival rate (both 2-year and 10-year) progressively increased. Because cystectomy cases as well as unrelated deaths were excluded from this study, and the tumours resected or destroyed, the only existing pathology was the epithelial change. Furthermore, with the exclusion of unrelated deaths, the only existing pathology was able to exert its influence. Thus it seems reasonable to suggest that epithelial proliferation of the type seen in Figures 1, 2 and 3 was defensive. Earlier studies (Sarma, 1970, 1972, 1978) have shown that the pattern of incidence of epithelial hyperplasia in bladder closely resembled lymphoid reaction, which was defensive. Thus there is an agreeable correlation between the 2 changes.

Comparative Pathology

Could epithelial proliferation (reactive hyperplasia) in the body be defensive? Mechanical friction on an unaccustomed skin surface leads to blistering, *i.e.* tissue death, but prolonged minor friction leads to hyperplasia which is entirely local and confined to the affected site. This is obviously defensive in character. The same phenomenon may be seen with a variety of agents: irradiation, chronic discharges and eczematoid states, etc., suggesting its non-specific nature. Cervical mucosa near a pessary and buccal mucosa near an ill-fitting denture show similar hyperplasia as a local defence. This is not confined to skin and epidermoid surfaces alone; recent studies (Sarma, 1979) on the nature of epithelial hyperplasia in the colon with chronic colitis have shown it to be a defensive measure with a profound influence on disease activity. Thus there is extensive evidence that tissues exposed to a variety of adverse conditions show simple proliferation (hyperplasia) as a non-specific form of self-defence.

Hyperplasia and Neoplasia

Detailed examination of a few bladders bearing papillary tumours was enough to reveal a spectrum of epithelial changes ranging from uniform and focal proliferation through microscopic tumours to frank papillary carcinomas (Figs. 1, 2, 3 and 4). The smallest tumours (Figs. 3 and 4) received particular attention and were examined for possible clues to the transition from hyperplasia to neoplasia. However, no histological or cytological differences were found in the cells forming the tumours and the adjoining mucosa. What then transformed a simple proliferation into a neoplasm?

Table 1 shows that following local destruction, 31% of low grade and 34% of medium grade tumours recurred. Furthermore, most of the recurrences were in the same grade. In 44% with low grade and 58% with medium grade tumours, new tumours developed in various parts of the bladder. This clearly suggests that the cause of either recurrent or new tumours is not related to the tumours or their grade. Figures 6 and 7 show that a progressive increase in epithelial proliferation (hyperplasia) cannot be responsible for either local recurrence or new tumours. These results clearly point to a missing factor (or factors) as the causative agent (or agents), which lie outside the tumours as well as the epithelium.

Role of Vasculature

In Figure 3 the miniature papillary tumour with a cellular mass smaller than that of the adjoining foci has a sizeable arterial supply. Microangiography in healthy bladders showed that the mucosa had no regular blood vessels of its own and relied for survival on simple diffusion, but that here and there aberrant vessels arose from the submucous or the intramural plexus to supply localised areas.

Figure 10 shows the microangiography in a bladder that had been the seat of multiple papillary tumours. The submucous plexus extended into the mucosa itself and showed several tortuous vessels. The overlying mucosa was histologically normal, strongly suggesting primary arterial growth. A segment of an artery which increases in length within a confined space can be accommodated only by assuming a helicine appearance. Figure 12 shows a large artery arising from an even larger artery in the submucous plexus and proceeding to supply a small tumour. Up to the base of the tumour it has a helicine appearance and within the tumour its branches are straight. Again, this suggests primary arterial growth underneath a normal or hyperplastic mucosa of the type seen in Figure 10; within the tumour the growing vessels and the tissue they feed are in equilibrium. This is a perfect example of a symbiotic growth relationship. A similar feature may be seen in smaller tumours (Fig. 11) and more dramatically in larger tumours (Figs. 13 and 14)—all pointing to the arterial growth having preceded the development of the tumours.

It seems reasonable to suggest, therefore, that the underlying arterial growth, by conferring autonomy from the rest of the mucosa, has transformed an area of simple proliferation (hyperplasia) into a neoplasm. These aberrant vessels, by supplying localised areas with exclusive and richer nourishment than the rest, provoke cellular proliferation, and the proliferating cells in turn stimulate arterial growth—setting up a vicious circle. Thus the reactive hyperplasia has been converted into reactive autonomy. Epithelial hyperplasia in the bladder and elsewhere was found to be defensive. Thus a neoplasm has unwittingly developed as a defence reaction.

It is natural for arteries, but not for tissues, to branch as they grow. This explains the frequent occurrence of tumours near the ureteric orifices—the sites where inferior vesical arteries enter and branch, and the sites of frequent aberrant vessels. The cellular masses forming the tumours in Figures 3, 4 and 5, far from being the masters of the growth process, are in fact the victims, and are controlled by feeding arteries. Together they represent an autonomous growth unit unrelated to any function. The hyperchromasia and mitotic figures which characterise the neoplastic process (Figs. 4 and 5) are mere expressions of rapid cellular proliferation brought about by the prodigious supply of nutrition.

On the other hand, simple proliferation (hyperplasia), unaccompanied by growth-prone blood vessel/vessels, fails to develop into a papillary tumour. Figure 15 shows a bladder that had been the seat of *in situ* carcinoma for over 2 years, and unfailingly showed exfoliated malignant cells in the urine. The mucosa showed a granular appearance on cystoscopy and papillary formation on histology, but even after a follow-up lasting more than 2 years no papillary tumours developed. Figures 16 and 17 show the absence of growth-prone arteries in the papillary processes and a consequent failure to establish the symbiotic growth relationship mentioned above.

Comparative Oncology

Can papillary tumours in the body result from symbiotic growth between aberrant blood vessels and either normal or hyperplastic epithelium?

The colon and rectum are the only other organs in the body where tumours with a comparable histology and identical behaviour occur with any frequency. For some obscure semantic reason they have been called "polyps". Recent studies (Sarma, 1979) with colonic angiography in health and in colitis have shown the following:

1. In health the colonic arteries are end-arteries, and the mucosa does not normally contain vessels larger than 0.3 mm in diameter.
2. In chronic colitis the pattern is distorted because of irregular arterial growth.
3. The pedicle or base of the "polyp" shows abnormal vessel or vessels—there is no "polyp" without them.
4. "Polyps" arise as a result of a symbiotic relationship between growing aberrant arteries and localised areas of either normal or hyperplastic epithelium.

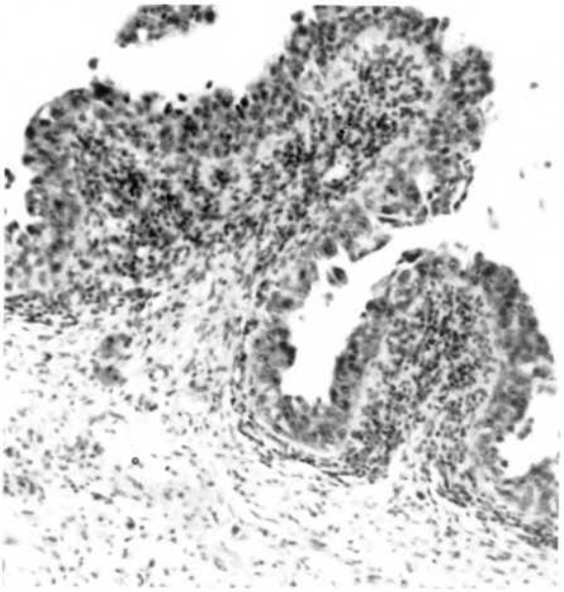

Fig. 16 Papillary processes only—no blood vessels (H and E × 130).

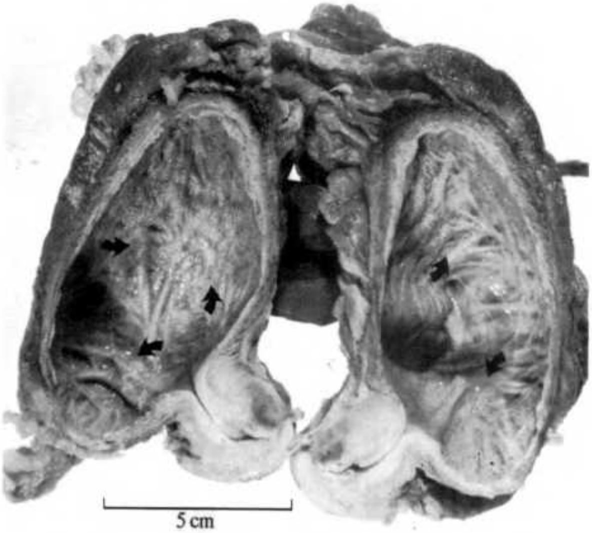

Fig. 15 *In situ* carcinoma of bladder. Note extensive granularity of the mucosa, but no actual papillary tumours despite a follow-up of over 2 years.

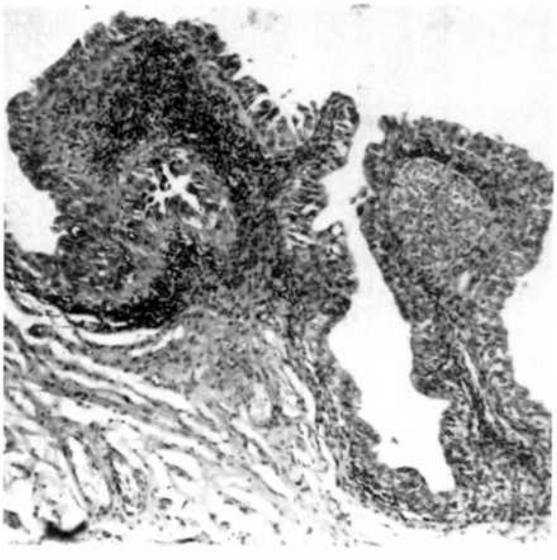

Fig. 17 Papillary processes that cannot develop into full-blown tumours. Note degenerating central cells and early cyst formation (H and E × 104).

It is concluded that epithelial hyperplasia seen in the bladder is a non-specific defensive reaction which represents the general phenomenon of tissue response to a variety of adverse conditions.

Bladders bearing papillary tumours show abnormal arterial growth which precedes the development of tumours. These arteries seem to confer autonomy to localised areas of either normal or hyperplastic epithelium, and provoke the growth process.

Papillary tumours result through such an accidental development of a symbiotic growth relationship between aberrant arteries and areas of either normal or hyperplastic epithelium.

Acknowledgements

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Microangiography of the Bladder in Health

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Summary—Microangiography of the bladder has been studied by the use of a mixture of Micropaque and Hypaque. There appears to be a considerable variation in the vascular supply, not only in different specimens but also in different parts of the same specimen. In general, the base and the lateral walls are more richly supplied than the rest. The vessels seem to form 3 plexuses: extramural, intramural and submucous. In places, moderately large aberrant vessels spring from the 3 plexuses and proceed into the mucosa itself.

The blood supply to the urinary bladder has been one of the least studied subjects in urology, although bleeding from this viscus under a variety of conditions has always been a source of anxiety to urologists. The small amount of relevant literature deals with only the source of main blood vessels and seldom describes the pattern of their ultimate distribution. Studies on the histogenesis (Sarma, 1970, 1972, 1978) of some of the well known pathological features, however, indicate the need to study the terminal radicles as well as the pattern of their supply to the mucosa itself. The aim of the present investigation has been to show the pattern of ultimate distribution of the vessels in the bladder wall and any regional variations.

Material and Method

The material for microangiography in healthy bladders came from post mortem examinations and was studied in 20 subjects known to have been free from any bladder disease. Amongst them 12 were male and 8 female, their ages ranging from 55 to 72 years.

Preparation of the Specimen for Injection

Mobilisation of the bladder was commenced anteriorly and continued laterally along the pelvic walls towards the posterolateral corners. The internal iliac arteries were identified, isolated and divided at their origins. The branches of the posterior division were ligated and divided distal to the ligatures. In female subjects the uterus was included with the bladder; the urethra and the vagina were divided close to the introitus. In male subjects it was found convenient to divide the membranous urethra and the rectum, thus completing a total pelvic exenteration.

The specimen was transferred to a dissecting table and spread out. With the aid of a small catheter passed through the urethra, the bladder was emptied and about 150 ml of buffered neutral formalin introduced. In large capacity bladders a larger volume was introduced in order to obtain a reasonable degree of firmness. The catheter was then removed and the urethra secured with strong linen. In female specimens it was found necessary to dissect the urethra from the vaginal wall before introducing the formalin.

Branches of internal iliac arteries not traversing towards the bladder were secured with linen ties. Considerable minute dissection and patience were required at this stage for a successful injection later. All open-ended vessels on the viscus were secured with under-running sutures to prevent leakage of the dye. Stoke-on-Trent cannulas were introduced into the internal iliac arteries and secured. Frequently, atheromatous plaques either partially or completely blocking the mouths of the anterior division of the internal iliac arteries made cannulation and injection difficult. These plaques should either be removed by endarterectomy or the cannulas advanced beyond the blockage. Sometimes it was found feasible, and indeed necessary, to cannulate separately the superior and the inferior vesical vessels.

Preparation of the Dye and the Injection

The dye used for arterial injection was a mixture of Micropaque and Hypaque. The Micropaque

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solution was thoroughly shaken and strained through 2 layers of gauze. At room temperature, 85% Hypaque forms a deposit of precipitate at the bottom, but when placed in water at 70°C for 20 min it dissolves to form a clear solution. When brought back to room temperature, such a solution remains unaltered for up to 10 min and mixes with Micropaque to form a stable homogeneous compound. By pipetting out the supernatant clear fluid, 85% Hypaque could be further concentrated with advantage. Equal parts of strained Micropaque and dissolved Hypaque were used for injection.

About 10 ml of such a mixture were gently injected into each cannula, taking several minutes in order to avoid rupturing the capillaries. Successful injection was indicated by the absence of extravasation and by the appearance of the dye in the surface vessels at remote sites. When extravasation occurred, the injection was discontinued and the leakage secured with under-running sutures. Completeness of the injection was checked by serial X-rays (Fig. 1). The whole specimen was then placed in a vessel containing buffered neutral formalin and allowed to fix for one week.

Preparation for Microangiography

After fixation the specimen was taken out and gently rinsed in a vessel containing water. Running water was avoided to prevent damage to the capillaries. The bladder was dissected clear from the rest of the organs and tissues. At this stage another X-ray was taken.

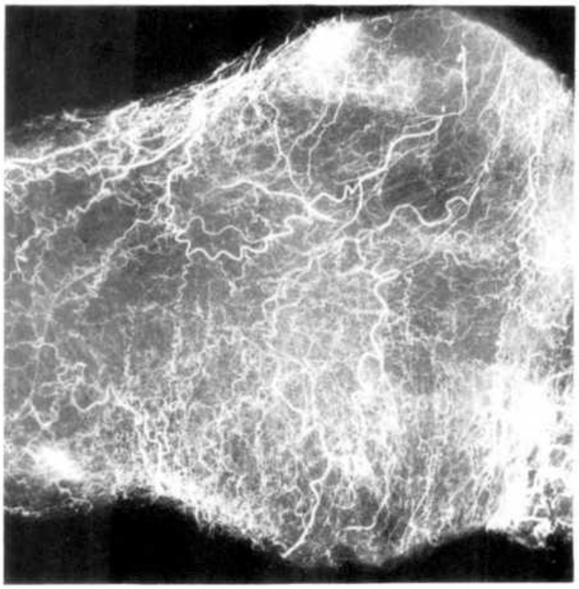

Fig. 1 Arterial injection and fixation of a healthy bladder. Post mortem specimen. Distension 150 ml.

The specimen was sectioned in the midline and the interior gently rinsed in a vessel containing water. Again running water was avoided. Both halves were cut into thin slices of 2 to 3 mm thickness with the aid of a carving knife—or preferably by circular saw. At this stage care was taken not to squeeze the dye from the specimen.

The slices were placed in their regular order on an Industrex—MX film and X-rayed under an industrial X-ray machine which, unlike ordinary machines, demarcated the musculature and the mucosa by their different densities. The developed film was thoroughly rinsed in distilled water, dried and examined microscopically under low power.

Results

The whole viscus seldom seemed to receive the arterial supply uniformly. The posterolateral walls —roughly triangular in shape with apices on the ureteric orifices—were more richly supplied than the rest (Fig. 1). The inferior vesical arteries enter the wall and branch about the middle of these areas. The posterolateral parts of the bladder neck and the adjoining anterolateral parts were moderately supplied. A broad midline band comprising the middle third of the trigone, the anterior and the posterior walls was, relatively speaking, avascular (Fig. 1).

Microangiography

Within the bladder wall, under low power microscopy the vessels were seen to form an intricate plexus which extended from the extramural plane through the musculature to the submucous region (Fig. 2). There was considerable regional variation in the density of the plexus: generally it was more dense in the posterolateral walls and the parts of the bladder adjoining the neck, and less dense in the midline anteriorly. Large areas of the mucosa had no direct arterial supply and seemed to be nourished through simple diffusion. This important point was better appreciated in the less distended specimens.

Under higher magnification the vascular plexus showed 3 distinct components—extramural, intramural and submucous, with free intercommunications (Figs. 3 and 4).

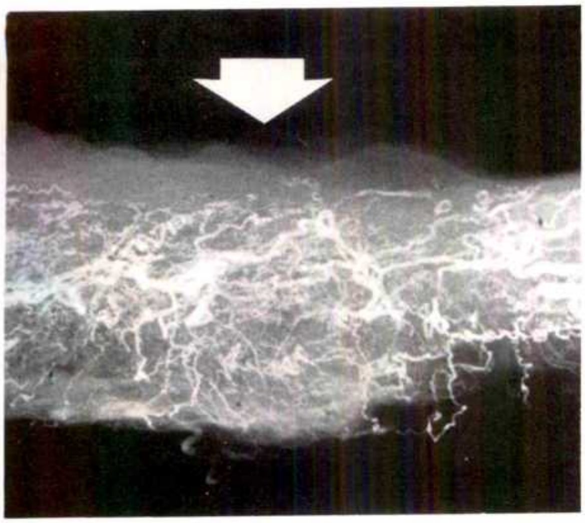

Fig. 2 Microangiography in a healthy specimen. White marker points to the mucosal surface. Distension 170 ml (× 12).

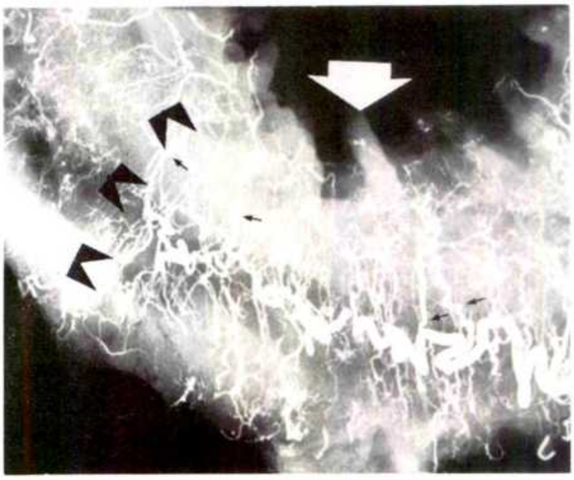

Fig. 4 Microangiography in health. White marker points to the mucosal surface. The 3 plexuses are clearly shown. A number of branches from the intramural plexus proceed to the mucosa. Distension 120 ml (× 12).

The Extramural Plexus

This was formed through anastomosis between branches of the superior and the inferior vesical arteries, as well as the prostatic branches of the internal pudendal and the middle rectal arteries. In females, vesical branches of uterine arteries replaced the prostatic component in the plexus, and generally appeared to be smaller than the male counterpart. It was situated on the outer surface of the detrusor and was generally prominent over the posterolateral walls of the bladder and the posterolateral sides of the bladder neck. Vessels larger than 0.5 mm in diameter were frequently seen in this plexus. Twigs from the extramural plexus pierced the muscular layers to establish communication with the intramural and the submucous plexuses. Sometimes, sizeable aberrant vessels from this plexus seemed directly to supply localised areas of the mucosa (Fig. 4).

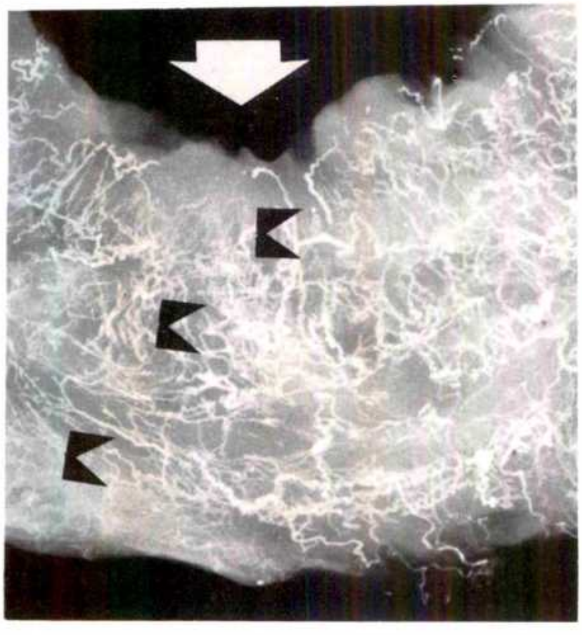

Fig. 3 Microangiography in health. White marker points to the mucosal surface. Extramural, intramural and submucous plexuses are clearly shown. Distension 150 ml (× 16).

The Intramural Plexus

This was formed by anastomosis between branches of the superior and the inferior vesical arteries as well as the efferent vessels from the extramural plexus. It was situated within the muscular wall and frequently extended into the submucous region. This plexus was prominent not only in the posterolateral walls but also around the bladder neck and the adjoining parts of the anterolateral walls. Arteries larger than 0.5 mm in diameter were quite frequently seen (Fig. 5) and efferent vessels from this plexus traversed towards the mucosa, but usually seemed to end abruptly by splitting into arterioles and capillaries in the submucous region (Fig. 4). Occasionally some of them reached the mucosa itself (Figs. 5 and 6).

The Submucous Plexus

This was almost a continuation of the intramural

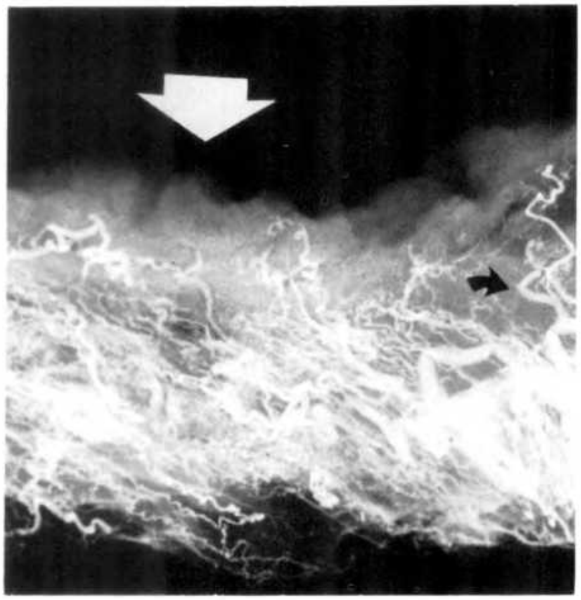

Fig. 5 Microangiography of bladder in health. White marker points to the mucosal surface. Note a sizeable aberrant artery arising from the vessel in the submucous plexus. Distension 150 ml (× 12).

plexus, and under low power microscopy appeared as the mucosal surface of the intramural plexus (Fig. 2). Here the vessels pursued a characteristic course parallel to the overlying mucosa, but under higher power some capillary-sized vessels (0.3 mm in diameter) could be seen to reach the mucosa itself (Fig. 3).

The Mucosal Vessels

There was considerable variation in the blood supply to the bladder mucosa, where large areas were either avascular (Fig. 2) or had at best some capillaries here and there (Figs. 3 and 4). Occasionally, vessels larger than 0.4 mm in diameter—either solitary (Fig. 5) or a leash of them (Fig. 6)—seemed to spring from large intramural or extramural arteries and proceed directly to the mucosa. These aberrant vessels were seen most frequently in the posterolateral walls and the adjoining parts of the anterolateral walls, occasionally around the bladder neck but seldom in the midline band, and are of considerable importance in the histogenesis of some of the pathological features (Sarma, 1981).

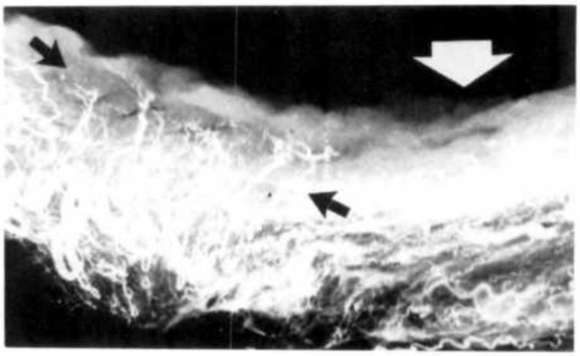

Fig. 6 Microangiography in health. White marker points to the mucosal surface. Note a leash of aberrant vessels from the intramural plexus going directly into the mucosa itself. Distension 150 ml (× 8).

A study of the blood supply to the urinary bladder showed considerable regional variations. The vessels formed 3 intercommunicating plexuses. Large areas of the mucosa seemed to receive nourishment through simple diffusion, supplemented by stray capillaries here and there, but in some areas—mostly in the posterolateral walls and the adjoining anterolateral walls—there were large mucosal vessels. The influence of these regional variations on the histogenesis of some bladder tumours has been discussed separately (Sarma, 1981).

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Urinary Continence in Children with Neurogenic Bladders

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Summary—Seventy-three children with neurogenic bladder dysfunction were assessed for urinary continence over periods ranging from 6 months to 4 years.

Acceptable continence was achieved in 35 (48%), the majority by means of intermittent clean catheterisation, usually with drug manipulation. Two children had to be diverted purely for intractable incontinence. A plan of management for children with neurogenic bladder dysfunction is described.

The management of the urinary tract of children with neurogenic bladders has passed through 3 broad phases. Prior to 1950 these children were largely left to their own devices, so that the majority of them were almost continuously wet. Published series testify to the fact that only about 3 to 23% of children with congenital neurogenic bladders develop spontaneous continence (Smith, 1972; Diokno *et al.*, 1976; Brereton *et al.*, 1977).

Between 1950 and 1972 many authorities were advocating urinary diversion, usually between 2 to 6 years of age and most commonly by means of an ileal conduit (Mebust *et al.*, 1969; Smith, 1972). This was thought to be the treatment of choice for all 3 of the major urological complications of children with congenital neurogenic bladders, *i.e.* for the deterioration of the upper tracts, for the social incontinence and for the recurrent urinary infections. Some authors (Smith, 1976) still maintain that early ileal conduit diversion is the best treatment. Recent publications, however (Schwartz and Jeffs, 1975; Light *et al.*, 1977) indicate that the ileal conduit is not without its complications and that as many as 56% of normal kidney units before diversion may show deterioration on long-term follow-up. Furthermore, it is now realised that other less drastic and somewhat more physiological procedures may be employed in many patients to overcome the problem of incontinence and malodour.

In 1972 Lapides popularised the concept of intermittent clean catheterisation (ICC) and this, together with drug manipulation, has become the standard method of obtaining urinary drainage in many centres (Lapides *et al.*, 1972; Mulcahy and James, 1979).

This study is the sequel to a preliminary report (Light and van Blerk, 1977) from a Spinal Defects Clinic wherein the majority of patients were on intermittent clean catheterisation. It reports the degree of success currently being achieved, the reasons for this and suggests methods to improve the results.

Patients and Methods

One hundred and six patients are currently being regularly seen and followed at the clinic. Of these, 29 have had urinary diversions and 77 are using their neurogenic bladders. The present study is concerned with 73 of these patients, 38 girls and 35 boys (age range 3-7 years). Two of the patients with urinary diversion are included in the series because they were diverted for intractable incontinence not responding to more conservative measures. The remaining 27 patients had their diversions either when it was the policy to divert at an early age or because of deteriorating upper tracts. Six of the 77 patients using their neurogenic bladders are excluded from the present study because they are below 3 years of age and continence cannot be assessed at this stage.

The sex, age distribution and aetiology of the spinal defect are shown in Table 1. Most patients (54) are on intermittent clean catheterisation, 5 are emptying their bladders by means of Credé

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Table 1 Analysis of 73 Spinal Defects

Sex	
Male	38
Female	35
Age	
3-17 years	
(Mean = 9 years)	
Aetiology	
Myelomeningocele	65
Sacral agenesis	3
Trauma	3
Transverse myelitis	1
Tuberculosis	1

expression and 4 are attempting to void spontaneously. In 10 patients these conservative methods have been abandoned; 7 males wear a penile appliance, one female is on continuous catheter drainage and 2 females have had urinary diversions by means of a colon conduit.

The method of intermittent catheterisation is similar to the routine advocated by Lapides *et al.* (1972) and has been fully described in the previous report (Light and van Blerk, 1977). At present there are 12 male and 6 female patients who carry out self-catheterisation. Two of these females are using the newly designed catheter recently described by Porteous (1980) with great success. This is made of "plexi-glass" (a transparent inert and rigid substance) and consists of the catheter with an attached handle which makes for easy insertion in females.

Altogether, 57 patients in the present series have had urodynamic evaluations. Using a CO_2 cystometer a resting cystometrogram was performed and the maximal urethral pressure was measured in each case. The bladders were defined as either hyper-reflexic or areflexic and the maximal urethral pressures were divided arbitrarily into 3 groups: low pressure 0 to 40 cm of water, medium pressure 41 to 60 cm of water and high pressure greater than 60 cm of water. The detailed technique and results of this study have been reported separately (Light *et al.*, 1978). Pro-Banthine, an anticholinergic, was used for the hyper-reflexic bladders and ephedrine chloride, an alpha-adrenergic stimulator, for those with a low maximal urethral pressure. Depending on the urodynamic evaluation, children who were using Credé expression or spontaneous voiding were placed on varying combinations of the above drugs as well as urecholine, a cholinergic, phenoxybenzamine, an alpha-adrenergic blocker and Valium, a striated muscle relaxant as indicated.

Excretory urography and voiding cystourethrography were performed on presentation and then at 6-monthly intervals until the child was 2 years of age. Thereafter they were performed yearly unless clinical conditions necessitated more frequent evaluation. The children were seen at least every 3 months and on each visit urine was obtained by catheterisation for microscopy, culture and sensitivity. Patients were not given routine prophylactic antibiotics. Each infection was treated accordingly. If severe recurrent infections occurred, the child was placed on long-term low dose antibiotic.

The follow-up period was from 6 months to 4 years.

Results

Degree of Success

Successful management was defined as a child who was always or mostly dry between manoeuvres to empty his bladder. The child was either completely confident of being dry both day and night and did not have to wear any protective clothing, or there was an occasional small leak which necessitated the use of a pad, but was insignificant and did not result in any social embarrassment or malodour. With this definition, 35 of the 73 patients were currently managed successfully (48%). When analysed according to the type of procedure used, 31 children were acceptably managed on intermittent catheterisation (57%), 3 on Credé expression (60%) and one by spontaneous voiding (25%) (Table 2). Only a small number of children were so confident of their continence that they required no protective clothing; 9 on intermittent catheterisation (17%), one on Credé (20%) and one on spontaneous voiding (25%).

Continence and Urodynamic Evaluation

Urodynamic evaluation was performed on 57 patients. As expected, the lowest rate of success

Table 2 Degree of Success

	No.	*Successful*	*(%)*
Intermittent clean catheterisation	54	31	57
Expression	5	3	60
Spontaneous voiding	4	1	25
Total		35	
Overall success		35/73	48

Table 3 Continence and Urodynamics (57 cases)

Bladder	*Sphincter*	*No.*	*Success*	*Success (%)*
Hyper-reflexic	Low pressure	9	2	22
	Medium	14	8	57
	High	9	5	56
Areflexic	Low	11	6	55
	Medium	8	3	38
	High	6	3	50
Total		57	27	

was achieved in patients who had the combination of a hyper-reflexic bladder and a low maximal urethral resistance. There were 9 patients in this category and only 2 were managed successfully (22%).

Theoretically one would expect the best results in children on intermittent catheterisation to be found with areflexic bladders and a high maximal urethral resistance. There were 6 such patients, 3 of whom are being managed successfully (50%). However, surprisingly, equally good results were found in the categories of areflexic bladders and low maximal urethral resistance (55% success), hyper-reflexic bladders with medium maximal urethral resistance (57% success) and hyper-reflexic bladders with high maximal urethral resistance (56% success) (Table 3).

Continence and Recurrent Urinary Infection

Recurrent urinary infection was defined as 2 or more positive urine cultures within 6 months in any child. This was present in 30 patients (41%). Of the 35 children managed successfully 15 had recurrent infections (43%) and of the 38 failures 15 had recurrent infections (39%) (Table 4).

Discussion

In view of the fact that only 3 to 23% of children with congenital neurogenic bladders develop spontaneous continence, whereas 57% of children in this series are being managed successfully on intermittent catheterisation and over 75% in other series (Diokno *et al.*, 1976; Mulcahy and James, 1979), it is apparent that this marked improvement is due to the institution of intermittent clean catheterisation as the basic method of urinary drainage. This method is simple, well accepted by the majority of patients and parents and is almost physiological in that the bladder is completely emptied at 3 to 4-hourly intervals. Adjuvant drug therapy, mainly with the anticholinergic Pro-Banthine to reduce uninhibited contractions and increase bladder capacity, and the alpha-adrenergic stimulator ephedrine to increase sphincter resistance, have further improved the results of intermittent catheterisation. Various surgical procedures are being developed which may extend the use of this modality even further.

Table 4 Continence and Urinary Tract Infection

		UTI	*(%)*
Success	35	15	43
Failure	38	15	39
	73	30	41

Drago *et al.* (1977) found a very good correlation between the urodynamic findings and degree of continence. Patients with areflexic bladders and high maximal urethral resistance were dry between each catheterisation, there was some improvement with the use of intermittent catheterisation where the intravesical pressures closely paralleled the maximal urethral resistance, and patients were continuously wet when the bladders were hyper-reflexic with small capacities. In the present series the poorest results were achieved when a hyper-reflexic bladder was associated with a low maximal urethral resistance, but good results were found with most other combinations of bladder and sphincter activity. Thus, although the urodynamic evaluation is a good guide to the basic detrusor and sphincter status, it should not deter one from initiating intermittent catheterisation in any patient. This investigation is, however, most useful in planning the exact pharmacological treatment which should be used with intermittent catheterisation.

Recurrent urinary infections occurred in 30 patients (41%). There was, however, no significant difference between patients who were managed successfully (15 patients, 43%) and those who were persistently incontinent (15 patients, 39%). One would expect a higher incidence of failure in those who develop recurrent infections, and especially in those with hyper-reflexic bladders, since the infection would promote uninhibited contractions; however, this was not substantiated in the present study.

From this analysis an outline for the urinary management of children with spinal defects has been adopted by our Spinal Defects Clinic (Table 5). These are overall guidelines only and each

Table 5 Outline of Urinary Management

0-3 years: No attempt to gain continence; protect kidneys:
ICC — Best. No drugs
or
Credé — If mother reluctant to do ICC
— Provided kidneys normal and no reflux.

3-9 years: Attempt to gain continence by conservative means:
ICC + drugs in usual dosages.
↓ if fails
— Urodynamics
— Drugs to maximal dosages
↓ fails, 6-7 years
Male—Penile appliance
Female—? indwelling catheter } Temporarily

9-11 years: Attempt to gain continence by surgical means in suitable cases, usually with ICC:
Males—Urethral compression operations
—Artificial sphincters
—? Stimulators
—Continent vesicostomy

11-13 years: If above methods have not succeeded:
Colon conduit

NB Progressive renal deterioration in spite of conservative treatment, do colon conduit at whatever age.

child is managed according to his particular physical, psychological and social needs.

In children under 3 years of age no attempt is made to achieve continence and the sole aim is to prevent renal deterioration. At this stage no detrusor or sphincter modifying drugs are used. Initially the child is placed on intermittent catheterisation as soon as possible after birth. This is advantageous to the child, for in most cases it reduces the incidence of urinary tract infection and either prevents or reduces upper tract deterioration (Lapides *et al.*, 1976). It is also usually of benefit to the mother as she feels she is doing something positive for her baby's well-being. In some circumstances the mother may be reluctant to perform intermittent catheterisation initially and then, provided the kidneys are normal and there is no vesicoureteric reflux, she may use Credé expression. If, however, there is already evidence of upper tract damage, or if reflux is present, one should insist on intermittent catheterisation as far as possible.

Between the ages of approximately 3 and 9 years one should attempt to gain continence by conservative means. In the majority of children this will mean intermittent catheterisation together with drug manipulation, usually Pro-Banthine and ephedrine in the standard dosage. A few patients may be managed with intermittent catheterisation alone and very few, possibly between 3 and 23%, may be found to void adequately spontaneously or with drug manipulation alone. If success is achieved with any particular modality, then that method is continued for as long as it works.

If intermittent catheterisation and drugs in the standard dosage prove unsatisfactory, a urodynamic evaluation is performed when the child is at a co-operative age. This is to categorise detrusor and sphincter activity and to ensure that the correct drugs are used. Thereafter, the drugs should be gradually increased until the maximum dosage is achieved. It has been found that surprisingly high doses can be tolerated and it is not uncommon for a child of 6 to 7 years of age to be on Pro-Banthine 30 mg 4 times daily. In this way a few more children may become continent on intermittent catheterisation.

If this fails to achieve the desired results, then at about 6 to 7 years of age one has to resort to a penile collecting device in males and possibly an indwelling catheter for females, in the hope that they are temporary measures only. Brereton *et al.* (1977) have found these to be satisfactory methods and they can certainly be used until the child is old enough for the next step.

Once the pre-pubertal years have been reached, usually between 9 and 11 years and, if all other methods have failed, then a more concerted surgical approach should be made in suitable cases. The patients most likely to benefit will be those who have an areflexic bladder with a low maximal urethral resistance. In these children it may be possible to construct a continent system which can then be drained by intermittent catheterisation. In males one may initially perform some type of urethral compression operation, such as those described by Kaufman (1972) or Hauri (1977). Ideally, as a first procedure one would like to achieve continence without implantation of foreign material. To date we have performed the Hauri procedure of separating the corpora cavernosa in the midline and embedding the urethra between them in 2 patients with initial excellent results. Two attempts at using the Rosen (1976) prosthesis were unsuccessful.

Another operation suggested in suitable cases is that of a continent vesicostomy. Here the stoma, which is situated on the abdominal wall, can be catheterised at regular intervals. One such procedure has been described by Schneider *et al.* (1975), in which a bladder flap is used to construct a tube and continent stoma, or one may use a technique similar to that of Kock (1973) by taking a loop of bowel from bladder to skin and constructing a nipple valve at the vesicointestinal anastomosis.

The use of stimulators to bladder, sphincter or spinal cord is not yet a practicality but may well become so within the next 5 to 10 years.

In females between 9 and 11 years of age the operations to consider are the continent vesicostomy or the urethral lengthening procedure described by Leadbetter (1964).

Finally, as a last resort, if all else fails, then around the time of puberty the urine should be diverted by means of a conduit. This is especially so in females and it is important not to delay beyond puberty because these patients are already suffering from a poor body image which becomes exaggerated at this time. At present it is generally accepted that the urinary diversion of choice is by means of the non-refluxing colon conduit (Richie and Skinner, 1975) in respect of reduced incidence of upper tract deterioration and stomal complications.

This graded outline of the urinary management of children with spinal defects has concentrated mainly on the problem of incontinence. It must be stressed, however, that if at any age the upper tracts are deteriorating and cannot be improved by conservative means, then the urine will have to be diverted, usually by means of a colon conduit.

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Intravenous Urography in the Follow-up of Carcinoma of the Bladder

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Summary—A urographic survey of 250 patients being followed for bladder cancer revealed 3 unsuspected ureteric tumours and 18 cases of ureteric obstruction. The tumours occurred in patients always affected by bladder recurrences and the obstructions were largely due to treatment of paraureteric bladder tumours by cystodiathermy or radiotherapy.

Regular follow-up intravenous urography is therefore unnecessary except in patients with frequent recurrences, but we advocate radionuclide renography as an essential, inexpensive screening test to rule out ureteric obstruction following the treatment of paraureteric tumours.

The indications for follow-up intravenous urography in patients who have previously presented with a primary transitional cell carcinoma of the bladder (TCCB) are questionable, but cystoscopic review alone fails to detect 2 serious complications that may subsequently arise in the upper tracts: the development of upper tract transitional cell tumours, and non-neoplastic ureteric stricturing resulting from previous treatment of the bladder tumours.

We wished to ascertain whether the intravenous urogram (IVU) was necessarily the most suitable follow-up investigation for the detection of these problems, when and how often it should be performed, or whether it could be replaced by simpler, cheaper alternatives.

Patients and Methods

Two hundred and fifty patients were studied who were already under regular cystoscopic review at St Paul's Hospital for a previous primary TCCB diagnosed before 1 September 1977. No patients were included who had had a previously known urothelial tumour of the upper tracts. There were 218 males and 32 females with an age range of 32 to 89 years (average 64 years). The patients had been under cystoscopic review from 3 months to 27 years with an average follow-up time of 8.7 years.

Follow-up IVUs had previously been performed with varying frequency, on average once every 6 years. As the patients entered the study, they had a cystoscopy and an IVU if one had not already been done during the preceding 12 months. Check cystoscopies continued at intervals of 3 to 12 months, depending entirely upon the local state of the bladder tumour. At the start of the study 76 patients (30.4%) had active recurrent TCCB and of these 40 (16%) had had recurrences present every year since their initial presentation.

To complete the second phase of the study, the IVU was repeated 12 to 18 months after each patient had entered the study.

Results

Two hundred and fifty patients entered the study and 190 completed it with a further IVU 12 to 18 months later. Sixty patients failed to complete this second phase owing to death (9), general ill health or infirmity (6), hospital transfer (4) or difficulty arranging IVUs on day case admissions (41).

The results were assessed under 2 main headings:

1. New findings in the upper tracts on the first study IVU.
2. New findings in the upper tracts on the second study IVU.

New Findings in the Upper Tracts on the First Study IVU in 250 Patients (Table 1)

Two patients had unsuspected, unilateral ureteric tumours: an invasive papillary and solid, intermediate grade TCC of the mid-ureter in one, and a multifocal, superficial, papillary differentiated

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TCC of the lower ureter in the other. Both patients underwent subsequent nephroureterectomy, but the former died from metastases within a year.

One patient had severe bilateral extrinsic obstruction of both ureters by local intrapelvic spread from a stage IV TCCB.

Ten patients had unsuspected, silent unilateral ureteric obstruction due to fibrous stricturing of the intramural ureter. This required resection and reimplantation of the ureter in 2 patients and a third underwent nephroureterectomy for gross hydronephrosis. Three further patients had severe post-obstructive atrophy of the kidney with virtual non-function and were not explored. Four patients had mild obstruction which did not require further intervention.

Incidental lesions such as renal cysts were discovered in a further 13 patients.

Table 1 New Findings in the Upper Tracts on the First Study IVU—250 Patients

Unilateral ureteric tumour	2
Bilateral ureteric obstruction by extrinsic TCCB	1
Iatrogenic ureteric orifice stricture causing:	
severe obstruction	6
mild obstruction	4
	13 (5.2%)
Incidental lesions:	
renal cysts	8
renal calculi	3
prostatic obstructive uropathy	1
abdominal aortic aneurysm	1
	13 (5.2%)

Table 2 New Findings in the Upper Tracts on the Second Study IVU—190 Patients

Unilateral ureteric tumour	1
Bilateral ureteric obstruction by a contracted bladder	2
Unilateral ureteric obstruction by a paraureteric TCCB	1
Iatrogenic ureteric orifice stricture causing:	
moderate obstruction	2
mild obstruction	1
Worsening of a known iatrogenic ureteric obstruction	1
	8 (4.2%)
Incidental lesions:	
renal calculus	1
abdominal aortic aneurysm	1
	2 (1.1%)

New Findings in the Upper Tracts on the Second Study IVU in 190 Patients (Table 2)

Of the 190 patients completing the second phase of the study, one was found to have a papillary transitional cell carcinoma at the pelviureteric junction; in retrospect this had been present on the first study IVU the year before.

Two patients had developed bilateral ureteric obstruction due to contraction of bladders previously treated with external radiotherapy.

One patient had developed unilateral ureteric obstruction due to a recurrent TCCB involving the ureteric orifice; the obstruction resolved after transurethral resection of the tumour.

Three patients had developed a new obstruction at the lower end of a ureter and one other had developed worsening of a known mild obstruction; all were due to fibrous stricturing resulting from previous cystodiathermy of tumours adjacent to the ureteric orifice several years earlier.

Incidental lesions had developed in a further 2 patients.

Discussion

Three (7.5%) of the 40 patients who had had active recurrent TCCB present every year since their initial diagnosis had unsuspected upper tract tumours, whereas none of the 210 patients with no active TCCB or only occasional recurrences had upper tract tumours.

The IVUs performed on the 250 cases at the start of the study revealed ureteric tumours in 2 patients and a third patient was found to have a tumour at the pelviureteric junction on the second study IVU; in retrospect this tumour had been overlooked on his first IVU. Of these 3 patients with upper tract tumours, 2 had presented 3 years earlier with a superficial papillary intermediate grade TCCB and one patient 12 years earlier with a well differentiated superficial papillary TCCB.

We therefore feel that all patients with active recurrent TCCB should continue to undergo annual radiographic screening to rule out the development of upper tract tumours.

The most frequent unsuspected upper tract complication was ureteric obstruction due to fibrous stricturing of the intramural ureter following the treatment of a TCCB involving or adjacent to the ureteric orifices; this had occurred in 10 patients on the first study IVU (Table 1). The tumours had been treated by open excision plus implantation of a radioactive element or external

Table 3 The Relationship of Ureteric Orifice Stricturing to All Previous Treatment—250 Patients

Type of treatment	*Number of cases of obstruction*			
	1st study IVU	*2nd study IVU*	*Previous IVUs*	*Total*
Open excision alone	—	—	1	1
Transurethral resection alone	1	—	2	3
Cystodiathermy alone	3 (3)	3	6 (2)	12 (5)
Cystodiathermy + external radiotherapy	—	—	2	2
Open excision + external radiotherapy	1	—	2 (1)	3 (1)
Transurethral resection + external radiotherapy	—	—	1 (1)	1 (1)
Open excision + radioactive implant	4 (2)	—	9 (2)	13 (4)
Reimplant of ureter into an irradiated bladder	1 (1)	—	—	1 (1)
Total	10 (6)	3	23 (6)	36 (12)

Figures in brackets = severe obstruction.

radiotherapy in 5, cystodiathermy alone in 3 and partial cystectomy with reimplantation of a ureter followed by external radiotherapy in one case. Only one case had been treated by a transurethral resection alone and the subsequent obstruction was only mild (Table 3).

On reviewing the IVUs performed on our patients before this study, the same trends were again very evident. Nineteen of the 23 patients who had previously had ureteric obstruction had had treatment involving cystodiathermy or radiotherapy to a paraureteric TCCB. Only 2 patients had had simple transurethral resection of tumour and in neither was the subsequent obstruction severe. Radiotherapy, either local or external, was also implicated in 4 of the 6 patients who had had severe obstruction resulting in functional loss of the kidney (5) or had required a ureteric reimplantation (1).

A review of the initial methods of treatment used in the 78 patients who had originally presented with a primary TCCB adjacent to or involving a ureteric orifice showed a similar relationship to the later development of obstruction (Table 4). Of 34 patients treated by simple transurethral resection only 3 developed mild obstruction, whereas 8 out of 17 patients treated by cystodiathermy became obstructed, 4 severely. Thirteen of the 17 patients treated by open excision of tumour plus implantation of a radioactive element (15) or external radiotherapy (2) developed obstruction, 5 being severe.

Tumour resection plus adjunctive radiotherapy, local in particular, and cystodiathermy therefore

Table 4 The Relationship of Ureteric Orifice Stricturing to the Primary Treatment of Paraureteric Tumours—78 Patients

Primary treatment	*Total*	*Obstruction*	
		Mild	*Severe*
Open excision alone	5	1	—
Transurethral resection alone	34	3	—
Cystodiathermy alone	17	4	4
External radiotherapy alone	3	—	—
Open excision + external radiotherapy	2	1	1
Transurethral resection + external radiotherapy	2	—	1
Open excision + radioactive implant	15	7	4
Total	78	16 (20.5%)	10 (13%)

appear to carry a much higher risk of causing strictures of the intramural ureter than resection alone. The majority of obstructions develop silently within a year and we therefore recommend that any patient who has had treatment for such a tumour, especially involving cystodiathermy or radiotherapy, should have a screening test performed within a year of the treatment to rule out obstruction; sporadic later examinations are also advisable.

A simple alternative to the IVU in detecting upper urinary tract obstruction is radionuclide probe renography, which has several advantages. The cost of a renogram is about half that of an IVU and the time taken is less. It causes little discomfort to the patient and the danger of an adverse reaction to iodinated contrast medium is avoided. A renogram is simple to perform and, more important, it is a far more sensitive detector of mild degrees of obstruction than the IVU.

Renography may also indicate the possible presence of upper tract tumours, since these tumours frequently cause obstruction. In the 2 series on ureteric tumours by Williams and Mitchell (1973) and Booth *et al.* (1980), 70% and 67% respectively of primary ureteric tumours produced urographic changes of obstruction or non-function of the affected kidney.

It is concluded that in the follow-up of patients with transitional cell carcinoma of the bladder it is not necessary to perform intravenous urography on an annual basis. However, 2 groups of patients run a considerable risk of developing serious upper tract complications.

All patients with frequent active recurrent TCCB require annual urographic screening to rule out the development of upper tract tumours.

We feel that all patients who have had treatment for a primary or recurrent TCCB involving or adjacent to a ureteric orifice should have follow-up radionuclide probe renography performed to rule out later ureteric obstruction.

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Hyperoxaluria Following Glycine Irrigation for Transurethral Prostatectomy

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Summary—Thirty-four patients were studied following transurethral prostatectomy with glycine irrigation during and soon after the operation. Three cases developed hyponatraemia and this was accompanied by severe hyperoxaluria with raised urinary glycolate. This could be a hazard if urinary volume were allowed to fall.

An adequate view of the prostate during transurethral prostatectomy (TURP) requires the use of an irrigating fluid. It is also customary in these hospitals to continue irrigation for 24 h after the operation. Pure water should not be used for bladder irrigation, since absorption through the prostatic venous plexus would cause intravascular haemolysis (Creevy, 1947). Saline cannot be used in conjunction with diathermy and therefore glycine solution has been recommended (Nesbit and Glickman, 1948) during the operation. Absorption of the glycine solution is known to occur very occasionally (Still and Modell, 1973) and leads to a fall in plasma sodium, and later to a fall in plasma osmolality. Since oxalate is one of the metabolic products of glycine, a high absorption of this amino acid might lead to hyperoxaluria (Crawhall *et al.*, 1959), possibly accompanied by raised urinary glycolate. We report a study on the effects of glycine irrigation during and after TURP upon urinary oxalate and glycolate excretion.

Patients and Methods

A series of 34 consecutive patients who had a transurethral resection of the prostate in one ward of St Peter's Hospital, London, was investigated. Each patient had pre-operative urea and electrolytes measured, in addition to full blood count, mid-stream urine culture (MSU), intravenous urogram (IVU) and chest X-ray. During transurethral resection of the prostate 3-litre bags of 1.5% w/v glycine solution were used to irrigate the prostate. Following the operation, each patient returned to the ward with a continuous irrigation of the same solution which continued for 18 to 24 h.

On the morning after the operation, blood was taken for urea, sodium, potassium and osmolality estimations. If the patient was found to be hyponatraemic, a 24-h urine collection for creatinine, oxalate and glycolate excretion was made after the continuous irrigation was stopped. Urinary oxalate was measured by an enzymatic method (Hallson and Rose, 1974) (normal range 0.1-0.5 mmol/24 h), and urinary glycolate was measured by a new enzymatic method (Kasidas and Rose, 1979) (normal range 0.10-0.35 mmol/24 h).

Three of the 34 patients (8.8%) were found to be hyponatraemic the morning after their operation, and in all of these the urinary excretion of oxalate was considerably elevated.

Case Reports

Case 1. G.C., aged 67, presented with a 2-year history of frequency, nocturia × 4 and gross hesitancy with a very poor stream. Physical examination was unremarkable apart from a firm, symmetrically enlarged prostate gland. Pre-operative evaluation revealed a normal full blood count, urea and electrolytes, MSU and chest X-ray. His IVU showed a trabeculated thick-walled bladder with a large post-micturition residue.

Transurethral resection of the prostate (40 g) was performed and this was later shown histologically to be benign. Four bags of glycine were used intra-operatively and a further 3 post-operatively. On the morning after operation his serum sodium dropped from 141 to 131 mmol/l and the 24-h urinary oxalate excretion was 0.97 mmol/24 h, with a glycolate excretion of 0.62 mmol/24 h. In the 48-h post-operative period he received 2 units of blood, 1 litre of dextrose-saline, 2 litres of normal saline, 1 litre of 5% dextrose and 1 litre of Hartmann's

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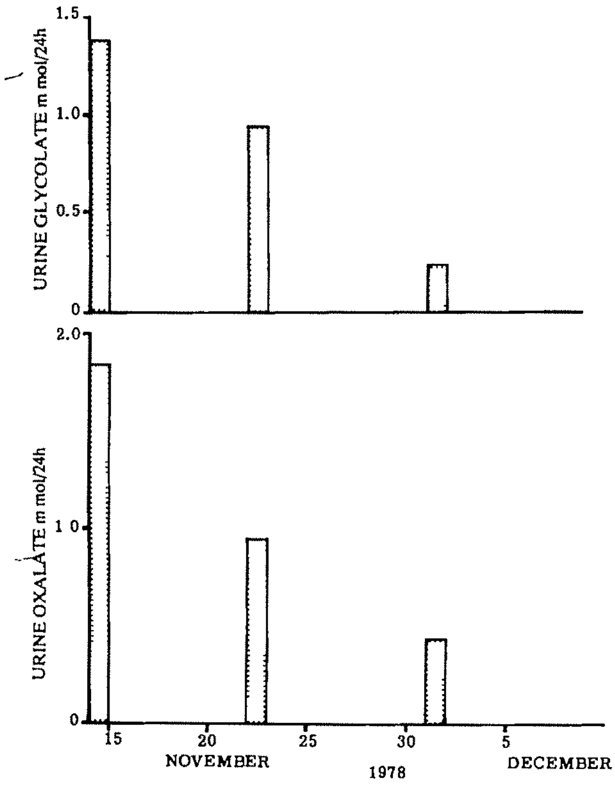

Fig. 1 Twenty-four-hour urinary oxalate and glycolate of case 2 measured on 3 occasions following TURP in November 1978. Upper limits of normal are 0.5 and 0.35 mmol respectively.

solution intravenously. He was discharged home on the fifth post-operative day and has since been discharged from the clinic, being asymptomatic.

Case 2. J.S., aged 68, was first seen in 1959 with chronic prostatitis. He presented again in 1978 with a history of one episode of haematuria in the preceding 2 months and steadily worsening frequency, nocturia, poor flow and hesitancy over the previous 10 years. He suffered from chronic bronchitis for which he took salbutamol, but otherwise his past history was irrelevant. Physical examination revealed a firm, symmetrically enlarged prostate gland. His pre-operative full blood count, urea and electrolytes, MSU and chest X-ray were normal. His IVU showed diverticula in a thick-walled bladder with a large post-micturition residue.

Cystourethroscopy revealed no evidence of bladder tumour and transurethral resection of the prostate (75 g) was performed (histologically benign). Eight bags of glycine were used intra-operatively and 3 post-operatively. He received intravenous infusions of 2 litres of normal saline, 1 litre of 5% dextrose and 1 litre of dextrose-saline in the next 24 h. Apart from a severe urinary tract infection post-operatively (caused by *Klebsiella aerogenes*) which was treated with cephalexin, he had a satisfactory result following surgery.

The biochemical results are shown in Figure 1. Post-operatively his serum sodium dropped from 140 to 130 mmol/l, and his osmolality to 258 mmol/l. His urinary oxalate was 1.84 mmol in the 24-h period following the irrigation with a urinary glycolate of 1.03, and the oxalate was still elevated (0.93 mmol) 2 weeks later (glycolate 0.92). It had returned to normal (0.43 mmol with glycolate 0.22 mmol) on the eighteenth post-operative day.

Case 3. W.P., aged 71, presented in 1978 with a history of 3 episodes of haematuria over the previous year and one episode of acute retention 3 months previously. On examination his prostate was enlarged. His pre-operative full blood count, urea and electrolytes, MSU and chest X-ray were normal, as was his IVU apart from a large post-micturition residue.

Cystourethroscopy revealed no evidence of bladder tumour and transurethral resection of the prostate (53 g) was performed (histologically benign), with no post-operative complications. Four bags of glycine were used intra-operatively and 2 post-operatively. In the 24 h post-operatively he received an intravenous infusion of 3 litres of dextrose-saline. His serum sodium decreased from 139 to 126 mmol/l and his urinary excretion was 0.97 mmol (urinary glycolate 1.08 mmol) in the 24 h after the irrigation was stopped.

Discussion

In the 34 cases studied, hyponatraemia was found in 3, and all of these showed gross hyperoxaluria in the immediate post-operative period. The incidence of this complication was therefore 8.8%, but it is probably significant that the cases show-

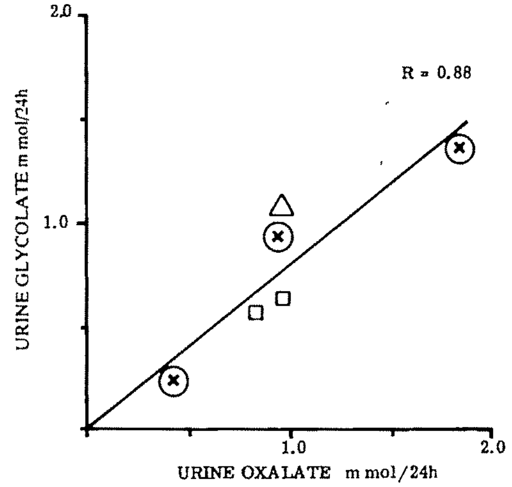

Fig. 2 Correlation between urinary oxalate and glycolate in the 3 patients with hyperoxaluria.

ing hyperoxaluria had large resections, when it might be more likely to open the venous plexus in the prostatic bed.

This finding of hyperoxaluria has not been previously described as a complication of glycine irrigation for TURP and raises a few points for consideration. Firstly, the degree of hyperoxaluria was very great, the 24-h excretions being of the same order as are seen in primary hyperoxaluria. Secondly, the raised oxalate excretion continued for up to 2 weeks, although steadily decreasing in severity, a period long enough to cause calcium oxalate deposition in the urinary tract or kidneys if a low urinary volume was allowed to occur. Fortunately, high fluid intake is normally encouraged after TURP, but if urinary volume were to fall for any reason in patients who had developed hyperoxaluria this could be a serious matter. Thirdly, although it seems obvious that the increased urinary oxalate arises from the glycine absorbed, some proof that this is so is provided by the finding of raised urinary glycolate. As seen in Figures 1 and 2, the excretions of the 2 organic acids rose and fell together, as would be expected if glycine was oxidised to glyoxalate, and thence to glycolate and oxalate (King and Wainer, 1968). Methoxyfluorane anaesthesia is a known cause of post-operative hyperoxaluria (Silverberg *et al.*, 1971) but this anaesthetic is not used in these hospitals.

In order to avoid the complication of hyperoxaluria after TURP it might be best to restrict glycine irrigation to the operation itself, and post-operatively to change to saline irrigation (as is, in fact, common practice). Investigations to establish this point are proceeding.

Postscript

Investigations have since been performed on 36 patients who had glycine irrigation intra-operatively and continuous bladder irrigation with normal saline for 24 h post-operatively. Five patients became hyponatraemic and 2 of these developed a marked hyperoxaluria (0.7 and 0.88 mmol/24 h respectively), with a raised urinary glycolate. It would seem, therefore, that the hyperoxaluria is due to intra-operative absorption of glycine.

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The Management of Transitional Cell Carcinoma in the Prostate

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Summary—Transitional cell carcinoma of the prostate is a rare tumour. A review of 318 patients with carcinoma of the prostate presenting to this hospital in the 5 years between April 1974 and April 1979 revealed 7 patients with transitional cell carcinoma arising within the prostate. Two of these had previously been treated for a transitional cell carcinoma of the bladder.

These prostatic tumours are usually poorly differentiated and carry a poor prognosis. Early radical surgery, however, achieved a good result in one of our patients. Other forms of treatment were ineffective and a review of the literature revealed that this was also the experience of others. We suggest that cystoprostatectomy should be considered as an early form of treatment.

Little or no consideration had been given to the origin of transitional cell carcinomas found within the prostate gland until Ende *et al.* reported 7 cases in 1963. The periurethral glands of the prostate are lined with transitional epithelium and they postulated that the tumour arose from them. The reported incidence of 1 to 4% of all primary prostatic carcinomas does not correspond to the small number of cases in the literature and suggests that in many centres there is a failure to consider this tumour as a separate clinical entity.

It is undoubtedly a manifestation of multifocal urothelial tumour in some patients and sometimes it is associated with a coexistent adenocarcinoma of the prostate. There are also patients in whom a transitional tumour has invaded the bladder base, urethra and prostate. It is therefore hardly surprising that the origin of the primary tumour is undefined in many cases.

In the majority of reported cases the prognosis has been poor, but in a few patients radical surgery has had more encouraging results (Greene *et al.*, 1976; Schellhammer *et al.*, 1977).

We were unable to find a reported series of this tumour in the English literature and have surveyed 7 patients with a transitional cell carcinoma arising within the prostate gland in order to question the efficacy of treatment.

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Patients and Methods

Three hundred and eighteen patients were diagnosed as having prostatic carcinoma in the 5 years between April 1974 and April 1979. Seventeen patients were reported to have a transitional cell tumour, but in 10 this had arisen in the urethra or bladder base mucosa, which excluded them from further consideration. Two further patients had a transitional cell tumour arising within the prostate but had previously been treated for a papillary bladder tumour. There had not, however, been any evidence of recurrence for the 2 years prior to developing the prostatic tumour in either patient. In 4 patients (1.2% of all prostatic carcinomas) a primary transitional cell tumour had arisen in the prostate gland alone, and one further patient had coexistent carcinoma *in situ* of the bladder. The main features are shown in the Table.

Presentation

The mean age at presentation was 63 (range 53-65); 6 of the patients had symptoms suggestive of obstructive prostatic disease and one of persistent cystitis. Two patients also complained of haematuria (Cases 4 and 7).

In 4 patients the bladder neck symptoms were associated with a palpable prostatic tumour on rectal examination, and 2 of these patients had a pre-existing adenocarcinoma. In the remaining 3 patients the prostate was clinically benign.

Table Presentation, Treatment and Outcome of 7 Patients With Transitional Cell Carcinoma of the Prostate

Patient	*Age at presentation with transitional cell carcinoma of prostate*	*Preceding tumour*	*Symptoms*	*Treatment*	*Outcome*	*Transitional cell tumour histology*
1	65	Nil	Cystitis	1976 cystoprostatectomy ureterosigmoidostomies + radical XRT	WELL no recurrence 40 months post-op.	Moderately differentiated
2	65	Transitional cell carcinoma bladder 6 yrs	Bladder outflow obstruction	1976 TUR 1976 radical XRT 1977 cystoprostatectomy ileal conduit	DIED 2 months post-op.	Poorly differentiated
3	65	Transitional cell carcinoma bladder 8 yrs	Bladder outflow obstruction	1976 TUR 1977 cystoprostatectomy ureterosigmoidostomies	DIED 1 month post-op.	Poorly differentiated
4	65	Adenocarcinoma of prostate 7 yrs	Bladder outflow obstruction + cystitis + haematuria	1974 TUR 1975 ureterosigmoidostomies 1975 radical XRT	DIED 3 months post-op.	Moderately differentiated
5	64	Adenocarcinoma of prostate 1 yr	Bladder outflow obstruction	1978 palliative XRT 1978 TUR	DIED of adenocarcinoma of prostate	Moderately differentiated
6	62	Nil	Occult tumour	1976 removed at retropubic prostatectomy	NO RECURRENCE at 2 yrs (died—myocardial infarction)	Well differentiated
7	53	Nil	Bladder outflow obstruction + haematuria	1979 TUR 1979 radical XRT	Treatment completed April 1979	Poorly differentiated

TUR = transurethral resection. XRT = X-ray therapy.

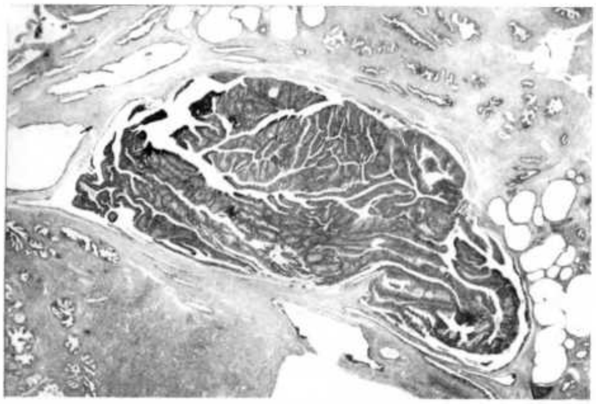

Fig. 1 Case 6. Section of prostatic tissue showing a large duct containing well differentiated transitional cell carcinoma. There was no tumour in the epithelium of the prostatic urethra and no pre-existing urothelial tumour (H and E ×80).

Diagnosis

The 5 patients who had symptoms of bladder outflow obstruction had a cystourethroscopy followed by transurethral resection of the prostate. Histology of the chippings then revealed transitional cell carcinoma. Case 6 had an occult transitional cell tumour found in a prostate enucleated for acute retention (Fig. 1).

One patient (Case 1) presented with a one-year history suggestive of cystitis which had been treated unsuccessfully by antibiotics. When he was referred to our department a histological diagnosis of carcinoma *in situ* of the bladder base was made.

There was endoscopic evidence of tumour only in the patient (Case 4) who had an adenocarcinoma of prostate that had invaded the bladder base.

In all 7 patients the diagnosis was unsuspected. It was not until the prostatic tissue was examined histologically that a diagnosis of transitional cell carcinoma of the prostate was made.

Treatment and Progress

Four patients eventually had a urinary diversion. In 3 this was a palliative procedure following incomplete transurethral resection and 2 had also been treated ineffectively with external pelvic radiotherapy. In each case radical radiotherapy consisted of 6 treatments over 18 days with a maximum tumour dose of 3,600 rads. No patient survived for more than 3 months following palliative surgery.

The fourth patient (Case 1) had an early radical cystoprostatectomy. Cystoscopy in this patient had revealed a basal cystitis and one of the bladder biopsies demonstrated carcinoma *in situ*. Both ureters were partially obstructed on the intravenous urogram and it was therefore thought that radiotherapy might increase the ureteric obstruction. A cystoprostatectomy with ureterosigmoidostomy was therefore performed. Unexpectedly, the specimen contained a moderately differentiated invasive transitional cell tumour clearly arising within the prostate. Despite very careful sectioning of the bladder base no continuity could be found between the abnormal bladder mucosa and the tumour within the prostate. The excision of the tumour was complete but radical external pelvic radiotherapy (maximum tumour dose 3,600 rads) was given post-operatively and the patient remains well 3 years later with no evidence of recurrence.

In no patient did external pelvic radiotherapy alone recognisably modify the course of the disease (Cases 2, 4, 5 and 7).

The patient with a well differentiated occult tumour that had been completely removed at retropubic prostatectomy (Case 6) had no further treatment and died 2 years later of myocardial infarction without recurrence of the tumour. Another patient (Case 5) died of widespread metastases from the preceding adenocarcinoma of prostate a few months after the diagnosis of transitional cell tumour was made.

Only 2 patients have survived for more than 14 months following the diagnosis of transitional cell carcinoma and in both of these cases it was possible to excise the tumour completely.

Discussion

Transitional cell carcinoma of the prostate probably constitutes 1 to 2% of all prostatic carcinomas (Ende *et al.*, 1963; Bates, 1969; Rubenstein and Rubnitz, 1969; Greene *et al.*, 1976), and we are in agreement with other authors that it is underreported (Ullmann and Ross, 1967; Tannenbaum, 1975). The variations of treatment within reported series confirm that no single regime of management has yet evolved.

Ende *et al.* (1963) suggest that the tumour arises from the transitional cells lining the ducts of the mucosal and submucosal glands of the prostate and therefore has a tendency for intraduct growth. Other authors (Franks and Chesterman, 1956; Ullman and Ross, 1967; Karpas and Moumgis, 1969) have described atypical, hyperplastic and dysplastic changes as well as carcinoma *in situ* and suggest that these changes may precede a prostatic duct tumour which then invades the

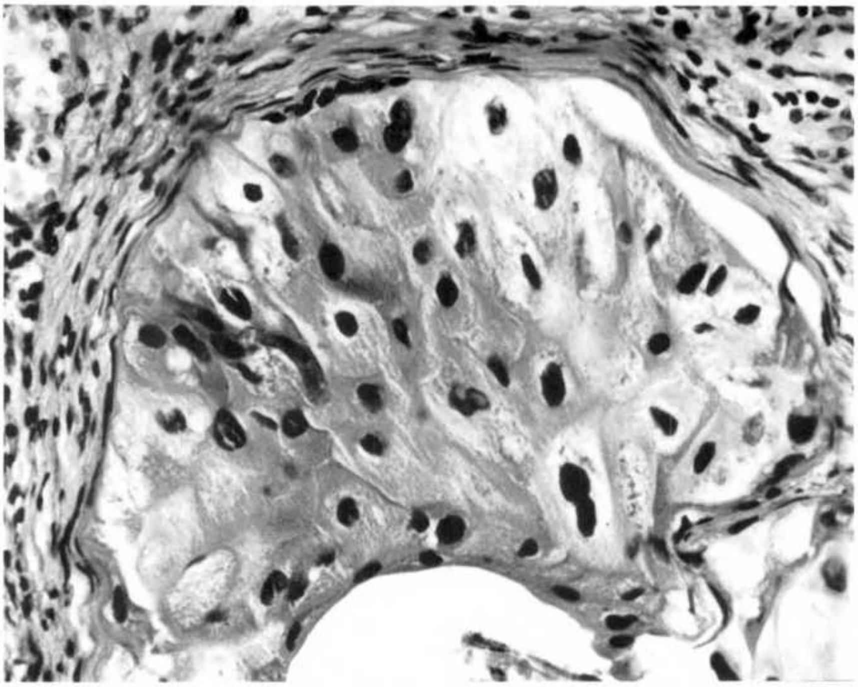

Fig. 2 Case 4. Intraduct squamoid transitional cell carcinoma (H and E × 500).

prostatic stroma. The squamoid appearance of the cells with the basement membrane apparently intact (Fig. 2) suggested to earlier workers that it was Bowen's disease (Melicow and Hollowell, 1952; Franks and Chesterman, 1956) or Paget's disease (Ortega *et al.*, 1953) of the urothelium, and it has been suggested by Karpas and Moumgis (1969) that the tumour arises from "reserve" cells lying between the luminal epithelium and the basement membrane.

There is, however, very little evidence to suggest that the aetiology is different from that of transitional cell tumours arising elsewhere in the urinary tract. Sometimes there is evidence of widespread urothelial dysplasia (*i.e.* atypical cellular nuclei) with areas of carcinoma *in situ* (Ortega *et al.*, 1953) as in Case 1. Similar tumours arise in patients who have been previously treated for a bladder tumour (Cases 2 and 3). This emphasises that a transitional cell carcinoma of the prostate is similar to other urothelial tumours, but does not preclude it from being treated as a separate clinical entity when considering management. We do not think that a preceding, treated, bladder tumour should alter the treatment of a separate transitional cell tumour arising within the prostate.

It is unlikely that the diagnosis will be made clinically, but most patients present with prostatic symptoms and these are sometimes associated with the signs of prostatic carcinoma. Either transurethral resection or transrectal biopsy will provide material for the diagnosis. Further management then depends on the clinical extent of the tumour.

It has been suggested that this tumour is less aggressive than adenocarcinoma of the prostate (Ende *et al.*, 1963; Bates and Thornton, 1966). However, our experience, and that of Rubenstein and Rubnitz (1969) and Johnson *et al.* (1972), do not support this premise. It is locally invasive and the majority of patients die with extensive pelvic infiltration. Since many tumours are poorly differentiated they soon infiltrate pelvic structures and radical treatment becomes difficult or impossible, but palliative urinary diversion will eventually be necessary in most patients. Despite this locally aggressive behaviour they rarely produce distant metastases. This suggests that early adequate ablation may be effective treatment. The tumour grows down the ramifications of the prostatic duct so that partial resection of the prostate is unlikely to be curative but occasionally, as in our patient who had a retropubic prostatectomy, local excision results in complete removal of the tumour. More radical surgery is usually necessary to excise the tumour totally.

La Plante and Brice (1973) found such a hopeless prognosis in patients with stromal invasion of the prostate from a bladder tumour that they considered prostatic invasion a relative contraindication to surgery. But this situation should not be confused with an isolated tumour in the prostate, when the prognosis might be improved by aggressive treatment.

No long-term results of radical surgery for this tumour have been reported, but in Greene's series (Greene *et al.*, 1976) there was a 3-year follow-up and their 2 survivors followed a radical prostatectomy and cystoprostatectomy. Shenasky and Gillenwater (1972) were also in favour of radical surgery on the basis of their 2 patients treated in this way. Our patient (Case 1) is free from recurrence 40 months after cystoprostatectomy.

The effect of surgery in these patients is confused by the fact that most patients also had radiotherapy. However, when radiotherapy was given alone it had little effect on our patients and this was also the experience of Johnson *et al.* (1972) and Greene *et al.* (1976). Hormone therapy has no place in the treatment of this tumour.

Kopelson *et al.* (1978) in a review of 58 cases claimed that radiotherapy was the treatment of choice in what they termed "periurethral prostatic duct carcinoma". Multiple histological variants were included in the study and both radiotherapy and hormone therapy were given. The radiotherapy details are somewhat indefinite and vary widely, so that no real conclusions can be drawn from this work.

No individual centre has sufficient experience to define the best form of treatment of this tumour with any certainty, but there is increasing evidence that a radical excision should be considered as soon as the diagnosis is made.

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The Effect of Local Hypothermia on Blood Loss during Transurethral Resection of the Prostate

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Summary—A prospective trial to investigate the effect of using cold irrigating solution during transurethral resection of the prostate was carried out. A control group of 44 patients was resected using irrigant at room temperature, and a trial group of 49 cases was resected using irrigant cooled to 2 °C. Blood loss during surgery was measured to see whether the cold irrigating solution had any effect on this loss.

There was a small reduction in blood loss in the cold group, but this reduction was not statistically significant ($0.5 > P > 0.3$).

Transurethral prostatic surgery is extremely safe, and the modern trend is for most prostatic surgery to be done endoscopically. There is no doubt that less per-operative bleeding would make the procedure even more acceptable to the surgeon and to the patient. The most dramatic reductions in per-operative blood loss have been reported using cooled irrigating solutions. However, the situation is not clear because investigators have published conflicting reports. Cockett *et al.* (1961) found no appreciable reduction in blood loss, whereas Serrao *et al.* (1976) reported that the blood loss was reduced almost 6-fold. We report our experience with cold irrigating fluid in a controlled trial.

Patients and Methods

Ninety-nine patients who had transurethral resection of the prostate gland over an 18-month period were selected for the trial. Excluded were patients with known cancer of the prostate, those who had had previous prostatic surgery, and those with known blood dyscrasias. Patients were divided into 2 groups, the control group being resected with irrigant at room temperature and the study group resected using irrigant cooled to 2°C. Patients were allocated to each group alternately.

The anaesthetic, in all cases, consisted of thiopentone, nitrous oxide, neuroleptic agents, pancuronium and Scoline, and was designed to have a minimal hypotensive effect. One surgeon (J.K.W.) carried out all resections and one anaesthetist (R.E.R.) gave nearly all of the anaesthetics.

The irrigant used was 5% mannitol, which was stored at 2°C in a specially constructed freezer. The temperature of the irrigant at entry to the resectoscope was measured. During the operative procedure the irrigating fluid was collected and at the end was well stirred and a sample taken for haemoglobin estimation. The total volume of irrigating fluid was measured. The haemoglobin estimation on the irrigating fluid was carried out using a calorimetric method based on the cyanmethaemoglobin principle. The prostatic chips were weighed in the unfixed state.

Two patients with unsuspected cancer of the prostate (nodule or larger) were excluded, as were 2 patients where the irrigant sample was mislaid. One patient was excluded because the irrigant sample clotted, and another where the telescope failed and no replacement was available for 20 min. Therefore 93 cases were available for study—44 controls and 49 trials.

Results

There was a wide range of resected prostatic

Table 1 Comparison of Variables Which Could Influence Blood Loss (Mean ± SD)

	Control (44)	*Cold (49)*
Mean prostatic weight (g)	18.6 (±14.7)	20 0 (±16.6)
Mean operating time (min) (includes anaesthetic)	54.2 (±20.2)	56.9 (±19.7)
Mean age (years)	65.0 (±9.8)	67.4 (±8.7)

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Table 2 Comparison of Blood Loss in Control (Warm) and Cold Groups (Mean ± SD)

	Control (44)	*Cold (49)*
Blood loss (g Hb)	42.87 (±42)	35.88 (±42)
Blood loss (ml)	289.6 (±288)	240.3 (±260)

weight in each group (Table 1): for the controls the range was 3 to 72 g (mean 18.61) and for the cold group the range was 3 to 85 g (mean 20.04 g). The difference between these groups was not significant.

The wide range of blood loss in both groups was reflected in the large standard deviations (Table 2).

In case the large resections with their associated larger blood loss were biasing the results, a subgroup of cases where the resection weight was 20 g and less was studied (Table 3). The mean prostatic weights in the control and cold groups of this subgroup of 62 cases are comparable.

The use of cold irrigating solution produced a reduction in blood loss in all groups (Table 4), but these small reductions were not statistically significant.

The mean temperature at entry of the irrigating solution in the warm group was 22.02°C and the mean temperature at entry for the cold group was 5.48°C.

Discussion

Blood loss during transurethral resection of the prostate depends on many factors, some of which can be standardised by proper trial design. The selection criteria for this trial were rigidly applied and a standard operation and anaesthetic were used. Only one surgeon was involved.

Cockett *et al.* (1961) studied 43 patients using cold irrigating solution and reported a small reduction in blood loss which was not statistically significant. However, the controls used by these authors were from another series of patients investigated by other authors. Robson and Sales (1966) investigated 156 patients (76 controls and 80 cold irrigation cases); 2 surgeons carried out these resections and it would appear that the control group was carried out first and the cold group later at a different hospital. These surgeons were residents in training, so that their skill in resection could have improved throughout the test period. It is also noted that these authors used a heat exchanger and were able to lower the irrigant temperature to 2.2°C at entry. This trial showed a 53% reduction in blood loss using cold irrigating solution and this was statistically significant ($P = 0.0025$).

Table 3 Comparison of Blood Loss in Control and Cold Groups in Resections 20 g and Less (Mean ± SD)

	Control (28)	*Cold (34)*
Mean prostatic weight (g)	9.8	10.8
Blood loss (g Hb)	22.83 (±25)	19.52 (±17)
Blood loss (ml)	145.5 (±156)	137.3 (±129)

Table 4 Statistical Significance of Reduction in Blood Loss in Cold Groups (Student's t Test)

	Difference from controls	*Statistical significance*
All resections	17% reduction	NS $0.5 > P > 0.3$
Resections 20 g and less	15% reduction	NS $0.5 > P > 0.3$

Serrao *et al.* (1976) studied 20 patients divided into 2 groups and found an almost 6-fold reduction in blood loss in the group irrigated with the cold solution. The numbers in this trial were small and the operations carried out by 2 surgeons. In addition, the method of allocation to the control or cold group is not mentioned and the type of anaesthetic is not described.

Using irrigant solution cooled to 2°C, we achieved a 17% reduction in blood loss but this was not statistically significant. It was not possible to store the irrigant at a lower temperature than 2°C without the bottles freezing up. The mean temperature at entry in this series was 5.48°C, which was warmer than the temperature at entry in the trial carried out by Robson and Sales (1966). Using a heat exchanger, they could lower the temperature at entry to a mean value of 2.22°C. It would seem, therefore, that the only way to obtain a very low temperature at entry to the resectoscope without a heat exchanger would be to lower the operating theatre temperature to extreme low levels, a measure that is unlikely to be acceptable. It is possible that with the extreme low temperature used by Robson and Sales (1966), blood loss could be reduced to a significant level, but it is doubtful whether the use of a heat exchanger would be justified, considering that the blood loss was reduced by only 53%.

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The Use of Cooled Irrigating Fluid for Transurethral Prostatic Resection

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Summary—Forty patients selected for transurethral prostatic resection (TUR) were randomly allocated to one of 2 groups. Irrigating fluid used in the first group of 20 patients was cooled to a constant 8°C; in the second group fluid at ambient temperature was used. Measurements were made of the volume of irrigating fluid used and haemoglobin loss during and after operation; the weight of resected tissue and its histological appearance were also studied. The core temperature of each patient was monitored throughout the operation.

Significantly less irrigating fluid was used in the group receiving cooled fluid. Although per-operative and post-operative haemoglobin loss was also markedly reduced in this group, the difference failed to achieve statistical significance. The clarity of the operative field was considerably improved by the use of cooled fluid.

Previous reports of attempts to reduce blood loss during TUR by local cooling have yielded conflicting results. Serrao *et al.* (1976) reported a 6-fold reduction in per-operative haemoglobin loss using irrigating fluid at 2°C, whereas Cockett *et al.* (1961) failed to show any benefit from using fluid at 3°C. As 25% of patients undergoing TUR require blood transfusion (Perkins and Miller, 1969), the possible benefits resulting from a reduction in blood loss are likely to be significant. A series of 40 patients was investigated, with strict control of irrigating fluid temperature in order to determine the magnitude of the reduction in haemoglobin loss achieved by the use of local hypothermia.

Patients and Methods

Forty patients selected for TUR by routine methods were randomly allocated to one of 2 groups. In 20 patients the irrigating fluid was cooled to 8°C by passage through a stainless steel coil immersed in a water bath and continuously monitored by a thermistor probe inserted into the fluid path just before it entered the resectoscope. The volume of the coil was less than 50 ml. A temperature of 8°C was selected following preliminary experimentation in which it had been found impossible to hold the resectoscope comfortably at lower temperatures. In the second group of 20 patients irrigating fluid at ambient temperature was used.

The operations were performed by 2 consultant urologists and a standard general anaesthetic with artificial ventilation was used. Epidural anaesthesia was not employed. The core temperature of each patient was monitored per-operatively using an oesophageal thermocouple.

During surgery all irrigating fluid which contained blood loss was collected and measured. An aliquot was subsequently analysed for haemoglobin concentration by means of an immunological assay using anti-human haemoglobin antibody, this being the most accurate method available, particularly for small concentrations of haemoglobin. Haemoglobin loss over the first 2 post-operative days was similarly measured; most patients had their catheter removed at this time. The weight of resected prostate was also recorded in each case, all prostates being histologically benign.

Results

Although haemoglobin loss, both during and after operation, was apparently reduced by approximately 25%, the differences between the 2 groups did not reach statistical significance when analysed by the Mann-Whitney U test for non-parametric data. The differences in haemoglobin loss per unit weight of prostate resected and per unit time likewise failed to reach significance, although again

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Table 1

	Mean per-operative haemoglobin loss (g)	*Mean post-operative haemoglobin loss (g)*	*Weight of resected prostate (g)*	*Volume of irrigating fluid (l)*
Cooled patients N = 20	11.4 (SD 14.2)	15.3 (SD 24.8)	7.5 (SD 4.3)	3.5 (SD 2.0)
Control patients N = 20	16.7 (SD 19.1)	21.6 (SD 32.4)	9.1 (SD 7.2)	6.2 (SD 3.0)
P value	>0.5 NS	>0.05 NS	>0.05 NS	<0.02

Table 2

	Mean duration of operation in min	*Drop in patients' temp. °C*
Cooled patients N = 20	18.3 (SD 6.3)	1.23 (SD 0.49)
Control Patients N = 20	25.9 (SD 8.9)	0.84 (SD 0.69)
Value	>0.05 NS	>0.05 NS

a favourable trend was demonstrated in the cooled group of patients. The volume of irrigating fluid used was reduced from an average of 6.28 litres in the control group to 3.83 litres in the cooled group, this difference being highly significant (Table 1).

Oesophageal temperature fell in the control group by 0.81°C on average and by 1.23°C in the cooled group, this difference showing no statistical significance. There was no difference in the mean operating time between the 2 groups (Table 2).

Discussion

The results suggest that both per-operative and post-operative haemoglobin loss from TUR may be reduced by the use of cooled irrigating fluid, although in this series statistical significance has not been achieved because of the wide range of haemoglobin losses experienced. In 2 patients the total loss was less than 1 g of haemoglobin, whereas 4 patients lost more than 100 g. It is thus possible that a larger series might have produced significant results, although it is interesting to note that significance was achieved by Serrao *et al.* (1976), using only 10 patients in each group. The significant reduction in haemoglobin loss was, surprisingly, only achieved per-operatively; no improvement was noted in post-operative loss, in contrast with our figures which show possibly a more uniform benefit.

The benefits gained by using smaller volumes of irrigating fluid are partly financial, but undoubtedly the surgeon benefits in being able to remove more prostate per unit volume of irrigating fluid used. It was felt, however, that the major advantage of this technique was the improved clarity of the operative field, a benefit which must unfortunately remain a subjective impression only. The technique has, however, been shown to be a safe and easy addition to routine procedure with, we feel, benefits to both patient and surgeon.

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The Urethral Syndrome: Morphological Studies

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Summary—Tissue removed at Richardson urethroplasty from 50 patients with the urethral syndrome, together with material obtained from the urethras of 44 cadavers, was examined in an attempt to elucidate the pathological basis for this syndrome. There was a significant increase in fibrous tissue in the urethrovaginal septum, accompanied by a loss of smooth muscle fibres and focal clumping of elastic tissue, in patients with the urethral syndrome.

The syndrome of recurrent dysuria, frequency, urgency and suprapubic discomfort is an important cause of morbidity in female patients of all ages. The aetiology of this urethral syndrome and the role of surgery in its treatment have been controversial. Richardson (1969), believing that a constricting ring of fibrous tissue acted as a mechanical barrier to normal micturition, introduced an external urethroplasty to overcome this. In a recent study (Splatt and Weedon, 1977), we confirmed the value of this procedure in 40 patients in whom other methods of treatment had failed to produce prolonged relief.

In order to study the pathological basis of the urethral syndrome, we have examined urethral and paraurethral tissue removed from a group of patients treated by the Richardson urethroplasty and from a group of age-matched cadaver specimens.

Materials and Methods

Tissue obtained at Richardson urethroplasty in 50 patients was pinned for orientation and fixed in formalin for later paraffin embedding. Sections from each case were stained with haematoxylin and eosin and by the Verhoeff-van Gieson method for elastic tissue and collagen. In 8 of these patients, a small piece of tissue was rapidly fixed in glutaraldehyde, embedded later in epon and sections stained with uranyl acetate and lead citrate. Ultrathin sections were examined in a Corinth 200 electron microscope.

In addition, material was obtained from 44 females coming to autopsy at the Royal Brisbane Hospital. The entire urethra and surrounding tissues were removed and fixed in formalin. Sections were taken along the urethra and from the urethrovaginal septum. They were paraffin embedded and handled in the same way as the surgical specimens above.

Results

Light Microscopy

Sections taken from the tissue excised at urethroplasty showed a moderate to severe reduction in

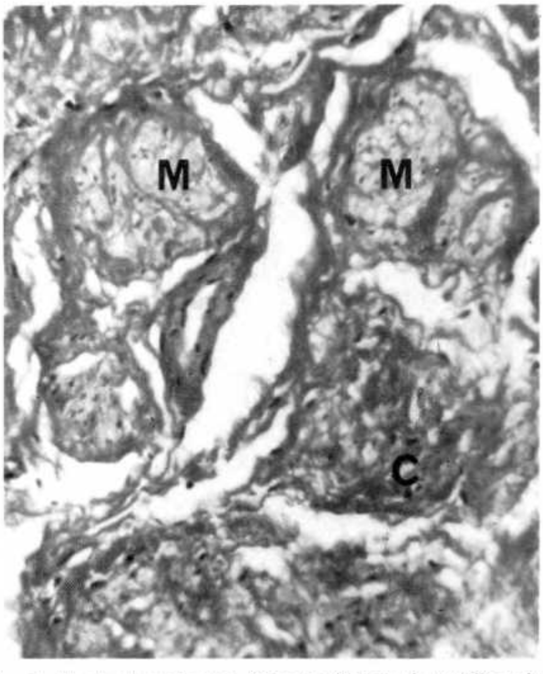

Fig. 1 Urethral syndrome. Note the fibrous tissue (C) replacing smooth muscle (M) in the periurethral tissue (Verhoeff-van Gieson ×240).

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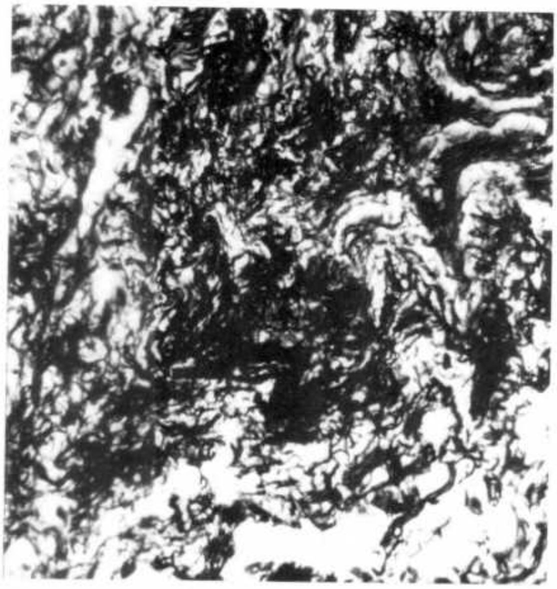

Fig. 2 Elastic tissue stain showing focal clumping of coarse elastic fibres admixed with collagen. No smooth muscle remains (Verhoeff-van Gieson ×240).

smooth muscle fibres and a corresponding increase in the amount of collagen. In places, dense collagen completely encircled surviving smooth muscle bundles (Fig. 1). Elastic tissue stains showed alteration of the normal network of fine fibres in close association with smooth muscle to a pattern characterised by coarse fibres irregularly clumped through the tissue. These collections of elastic tissue were most prominent towards the vaginal surface of the tissue removed (Fig. 2). In 8 patients with marked trabeculation of the bladder, these changes of fibrosis and elastic clumping were quite prominent.

Sections from the urethras of 17 cadavers with bladder trabeculation also showed significant fibroelastosis, but there was no apparent correlation between the degree of trabeculation and the severity of the fibroelastosis. In the remaining 27 cadavers there was no evidence at autopsy of bladder trabeculation. In these cases the urethras showed only mild fibrous replacement of smooth muscle, although there was a tendency for this to increase with the age of the patient.

Electron Microscopy

Ultrastructural examination confirmed the changes seen by light microscopy (Fig. 3). Smooth muscle cells, although reduced in number, were for the most part normal (Fig. 4), but in areas where there was abundant collagen the muscle cells showed a decreased number of myofilaments and surface caveolae.

Discussion

Our studies on patient and cadaver specimens

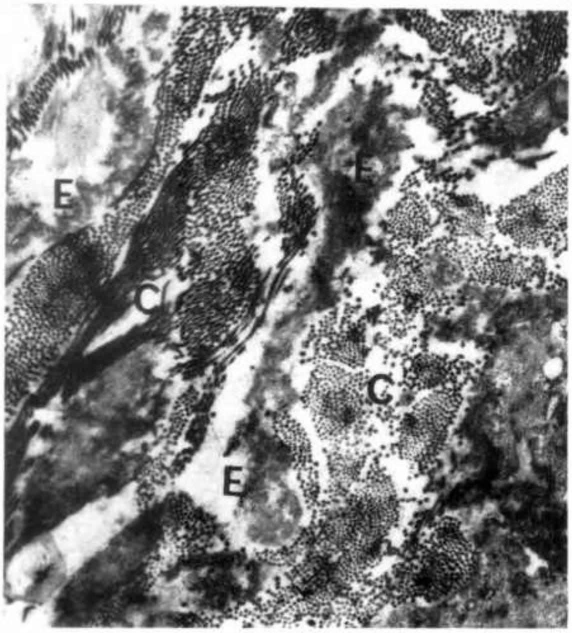

Fig. 3 Numerous collagen fibres (C) with coarse intervening elastic tissue (E). Note the absence of smooth muscle (×8000).

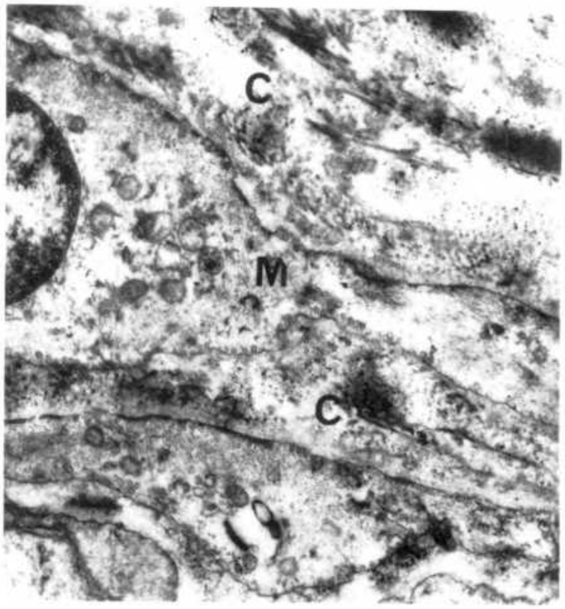

Fig. 4 An area of the urethrovaginal septum showing early changes only. A smooth muscle cell (M) is surrounded by collagen (C) bundles (×12,000).

have confirmed the findings of Woodbourne (1961) that the human female urethra is a myoelastic tubular extension of the bladder. We think that the elastic tissue which surrounds the smooth muscle acts as a tensile nexus to allow for a coordinated shortening and widening of the urethra during bladder contraction. Interference with this normal anatomic arrangement occurs in the urethral syndrome, where collagenous replacement of smooth muscle produces a non-compliant urethra. Evans (1971) first confirmed this increased quantity of collagen by measuring hydroxyproline values in the urethrovaginal septum of patients coming to autopsy with the urethral syndrome. The external urethroplasty described by Richardson (1969) was designed to excise this connective tissue which produced a urethral resistance to micturition.

The cause of this urethral fibrosis and elastic clumping remains an enigma. It has been suggested that it may be directly related to a diminished oestrogen effect, although the possible role of trauma and infection was also mentioned (Evans, 1971).

Our autopsy studies suggest that this increased fibrosis is, in part, age related, but it was also found in younger patients with the urethral syndrome and patients coming to autopsy with bladder trabeculation. The recent observation (Gosling and Dixon, 1978) that smooth muscle cells in the obstructed upper tracts may be involved in the manufacture of elastin and collagen in some circumstances may be relevant.

We were surprised at the number of patients who had some degree of bladder trabeculation at autopsy and the correlation that existed with the presence of fibroelastosis of the urethrovaginal septum. It is possible that many of these patients were asymptomatic although in a few, symptoms indicative of the urethral syndrome were recorded during life.

It is interesting to note that when the urethrovaginal septum is incised vertically and horizontally as a consequence of the inverted T-shaped incision made in the course of a Richardson urethroplasty, wide gaping of the incision occurs. This may result from an alteration in the various constituents of the septum as seen on histological examination, and is probably due to the tensile property of the elastic tissue which retracts when incised, which is the equivalent of transurethral incision of bladder neck contracture in the male. Indeed, so wide is the gaping that we have slightly modified the Richardson urethroplasty to making an inverted T-shaped incision only and not excising any tissue.

Our findings suggest that fibroelastosis constitutes a pathological basis for the urethral syndrome.

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Radionuclide Studies of the Lower Urinary Tract

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Summary—The results of prospective experimental and clinical studies into the use of radionuclides in the evaluation of urinary flow rates and residual urine volume estimations are presented.

The results indicate that the radionuclide estimation of flow rates is accurate, but complex and time-consuming compared with other available methods. The calculation of residual urine is simple and accurate where residual volumes are not extremely large.

The opportunity for such lower tract studies after renography should not be missed where clinically appropriate, and the combined upper and lower tract studies provide a useful quantitative urological profile.

Radionuclide studies have shown themselves to be of considerable value in the practice of clinical urology during the past 10 years. The majority of procedures have concentrated on renal imaging and function and upper tract urodynamics. Apart from vesicoureteric reflux studies and scrotal imaging, little attention has been focused on the role of radionuclides in the investigation of the lower urinary tract. Yet, following renography, the bladder contains a quantity of radioactive urine which might usefully be applied to 2 important lower tract measurements—flow rate and residual urine. This paper presents our investigations into the accuracy and value of such lower tract measurements.

Materials and Methods

Both flow rate and residual urine were investigated by experimental and clinical studies.

Flow Rate

Following radionuclide renography using ^{123}I-Hippuran or ^{99m}Tc-DTPA, flow rate can be measured on a dynamic gamma camera study by observing the rate of decrease of counts from the bladder region as the patient voids. This activity-time curve represents bladder volume and its derivative measures flow rate. The curves are calibrated by measuring the voided volume (Fig. 1a).

Experimental Study A reservoir containing saline and ^{99m}Tc-pertechnetate was set up in front of a gamma camera and above a standard Disa mictiometer. The reservoir was emptied at a varying rate into the mictiometer while a dynamic study of 2-second frames was taken on the gamma camera/computer system (Nuclear Data camera; Link Systems Gammascope). The resulting isotope flow rate and Disa curves were then plotted and compared.

Clinical Study Nine patients had flow rate studies using the gamma camera method, 7 with concurrent Disa estimations and 2 with Disa estimations on different days.

Residual Urine

Residual urine volumes can be measured by taking gamma camera images of the bladder before and after micturition. Counts remaining in the post-micturition picture are used to measure residual volume, calibrated in terms of the known voided volume.

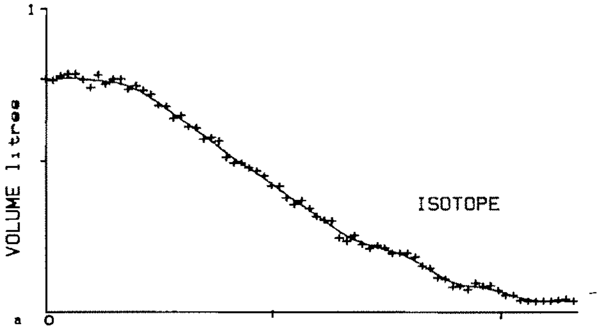

Fig. 1a Radionuclide bladder emptying curve from gamma camera study.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Experimental Study A 500 ml bag of saline containing ^{99m}Tc-pertechnetate was suspended in a water bath containing variable amounts of background activity; 50 ml increments of the radioactive saline were withdrawn from the bag and at each stage a one-minute static picture was taken. Bag and background areas of interest were defined and the residual volume calculated from the resulting counts. These results were then compared with the known volumes in the "bladder".

Clinical Study Eleven patients underwent the gamma camera study and were then catheterised to obtain an independent measure of residual volume. Two difficulties were experienced with the catheter measurement of residual urine. Firstly, it was not always certain that the bladder had been completely emptied by catheterisation. Secondly, there was an inevitable delay between finishing the isotope test and catheterisation. These patients were all well hydrated, having been given more than usual to drink for the purpose of the renogram and flow rate estimation. Thus it was necessary to make a correction for the amount of urine which had accumulated in the bladder during the delay period by estimating the urine production rate. This was done in all but 2 cases by leaving the catheter *in situ* after bladder drainage for a further period and measuring the amount of fresh urine which accumulated during this time.

Results

Flow Rate (Experimental Study)

Figure 1b shows an experimental flow rate study compared with simultaneous Disa flow rates. The 2 methods correlated well when the flow rate was reasonably constant, but because the isotope method had a slower response time, momentary peaks and troughs in the flow rate tended to be slightly underestimated.

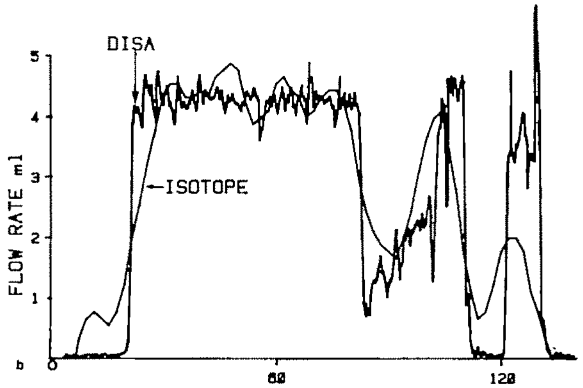

Fig. 1b Results of comparison between experimental radionuclide flow rate and Disa flow rate. Where the maximum flow rate is maintained for a few seconds, the methods correlate well. The radionuclide method response time is slower, however, and may underestimate momentary peaks of flow.

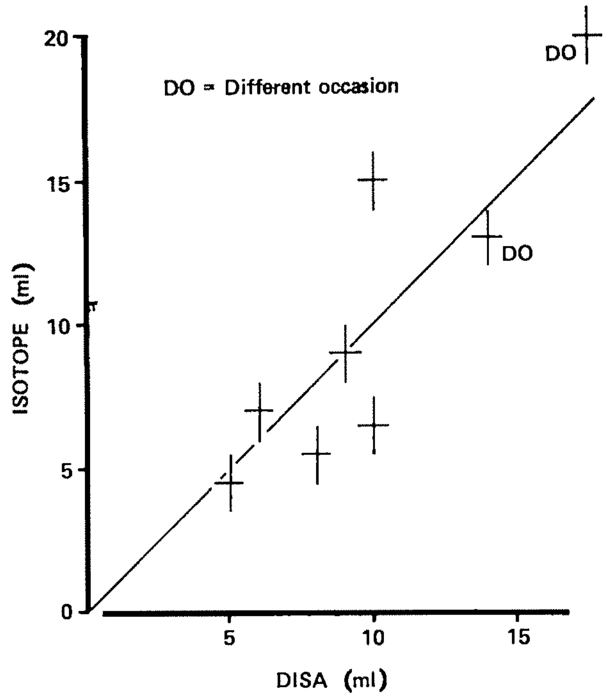

Fig. 2 Results of comparison of clinical radionuclide flow rate and Disa flow rate.

Flow Rate (Clinical Study)

Figure 2 shows the results in the 9 patients examined so far. There was broad agreement between the 2 techniques but, as in the experimental study, the Disa apparatus was better able to measure momentary peaks of flow. There was thus a tendency for the Disa result to be a little higher than the isotope rate, depending on the duration for which the peak was maintained.

Residual Urine (Experimental Study)

Figure 3 shows the results for 2 different count rates (or dosages) and 2 different levels of background activity. The accuracy with which residual urine can be measured can be seen to depend not only on these factors but also on the voided volume. For a valid isotope residual volume estimation, the voided volume needs to be at least as large as the residual volume and preferably double. Thus small to moderate residual volumes can be measured more accurately than high ones.

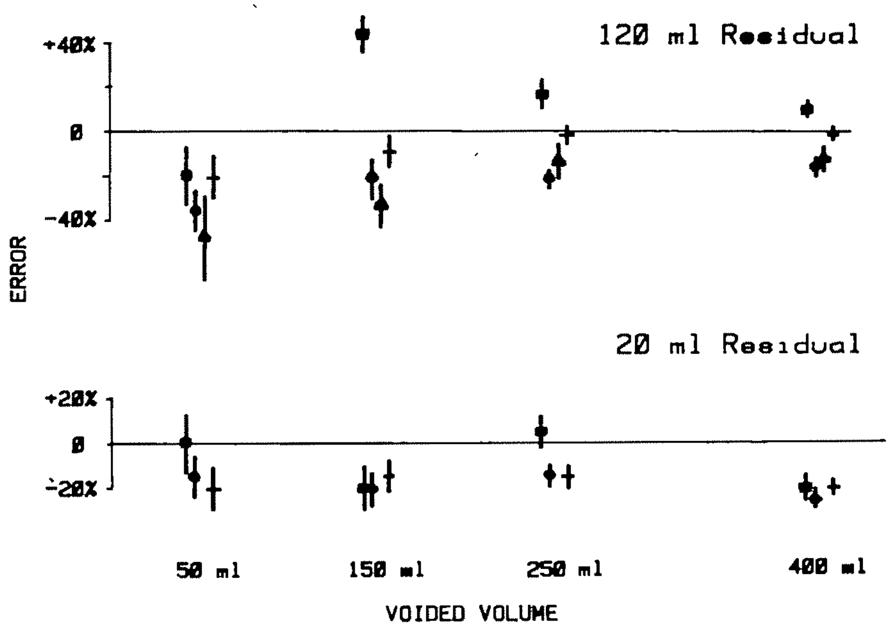

Fig. 3 Results of comparison between experimental radionuclide residual urine volume and actual residual volume. Where voided volume is twice or more residual volume, there is a high degree of accuracy, falling to poor correlation when voided volume is less than residual volume.

Residual Urine (Clinical Study)

The results (Fig. 4) complemented the experimental study. The 2 methods generally agreed, apart from cases where the residual urine was very large and only a small amount was voided, and apart from the one case where there was a long delay between isotope estimation and catheterisation. This resulted in a very dubious correction calculation and gave an estimated negative residual urine volume. This point demonstrated the need for scrupulous technique, and also the difficulty in being certain that catheter drainage was complete. The bladder in this case was clearly not emptied completely the first time, resulting in an erroneously high estimate of urine production rate and subsequent correction.

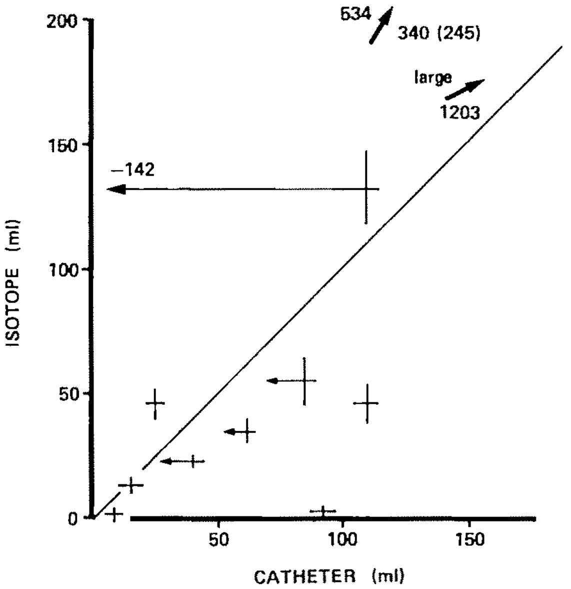

Fig. 4 Results of comparison between clinical radionuclide residual volume and catheter residual volume. Where residuals were huge, agreement was poor, but where residuals were at least less than voided volumes, correlation was good. (NB: intersections = precorrected values; arrows = corrected.)

Discussion

Interest, over the years, in the use of radionuclides in lower urinary tract studies has been limited. Mulrow *et al.* (1961) used ^{131}I-labelled Diodrast to measure residual volume, and Rosenthall (1963) later improved on this technique using ^{131}I-Hippuran. Winter (1964) suggested that the estimation of residual volume might be the final step in radioisotope renography. In spite of these papers and a report from Strauss and Blaufox (1970) on the use of ^{131}I-Hippuran and probe detectors to measure both flow rate and residual volume, nuclear medicine methods, particularly with a gamma camera, have not become widely used to study the lower urinary tract. This is understandable,

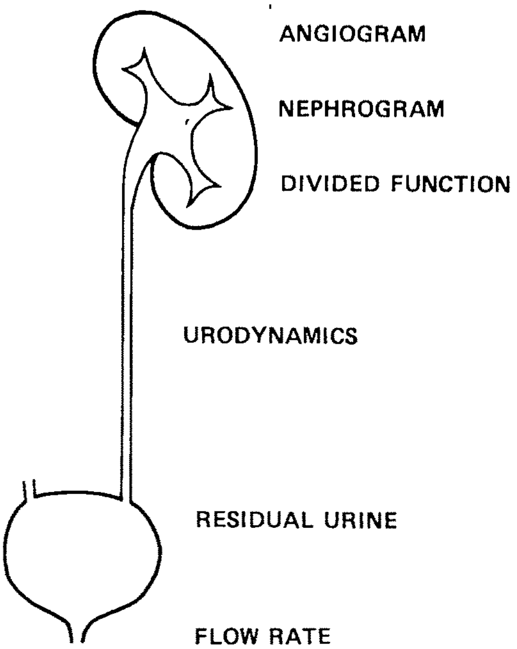

Fig. 5 The radionuclide urogram—information available from the single ^{123}I-Hippuran scintigram study.

since urodynamics has become established as a distinct urological subject in its own right, with its own equipment and technology. Nevertheless, sophisticated urodynamic centres tend to be restricted to major urological departments, while nuclear medicine has recently enjoyed an expansion resulting in gamma camera facilities in all major teaching hospitals and many district general hospitals. We decided therefore to bring these techniques up to date by applying the gamma camera and standard nuclear medicine computer system to the evaluation of flow rates and residual urine volumes.

Results

The results show that radionuclides can be used to obtain an accurate estimate of urinary flow rates by monitoring, after renography, the rate at which the isotope leaves the bladder during voiding. However, the methodology is rather complicated and somewhat time-consuming, and the resulting curves do not show the same detail and instantaneous fluctuations in rate which the Disa flow rate apparatus is capable of producing. These are eradicated in the smoothing operation necessary to eliminate statistical fluctuations during derivation of the curves. Simpler and more efficient means to measure flow rate exist, but radionuclides may be useful where such facilities are not available.

In contrast, the radionuclide estimation of residual urine is quick and simple. It is a useful further measurement after renography, as suggested by Winter (1964). The situation where it becomes inaccurate is in the patient with a large bladder volume who voids only a little urine and retains a large residual volume, for then the statistical error on the small change in bladder counts leads to large uncertainties in the residual volume. Nevertheless, the difference between, say, a residual volume of 800 ml and 900 ml may not be vital, and the existence of a considerable volume will be obvious anyway; the difference between a residual volume of 30 ml and 130 ml may be more significant and more important to quantify. At this end of the scale the radionuclide procedure is accurate to within about 10 ml.

Our conclusions are thus similar to those of Strauss and Blaufox (1970), using probe detectors 10 years ago, except that more convenient methods are now available to measure flow rates than were then in existence. Nevertheless, it is important to emphasise that, using radionuclide techniques, it is possible to obtain an isotope angiogram, parenchymal images, quantified differential renal function, upper tract urodynamics, urinary flow rate and residual urine. Such a urological profile is of considerable value as a non-invasive screening test, and the opportunity to complement the highly accurate upper tract studies with the bladder function tests should not be missed where it is clinically appropriate (Fig. 5).

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Unheralded Urinary Tract Infection in the Male
A Clinical and Urodynamic Assessment

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Summary—Fifty adult males presenting with unheralded single or recurrent urinary tract infections, but without prior urinary symptoms or disorders, were investigated by appropriate urodynamic techniques. Pressure/flow videocystography revealed significant underlying lower urinary tract abnormalities in 40 cases (80%) compared with only 11 (22%) whose abnormalities were also demonstrated by standard intravenous urography or endoscopy.

We suggest that videocystography is the most efficient diagnostic procedure for these cases in a specialist unit but recommend the intravenous urodynamogram as a simpler screening test for general use.

Urinary tract infections in the male are uncommon in the absence of bladder outlet obstruction. We wished to determine the incidence of significant, but latent, urodynamic abnormalities in patients presenting with unheralded single or recurrent attacks of infection in the absence of previous or concurrent symptoms suggestive of an underlying urodynamic disorder such as outlet obstruction.

Patients and Methods

A retrospective study was made of 50 consecutive male patients referred to our urology department because of a single or recent, recurrent attack of urinary tract infection in the absence of previous urinary tract symptoms or of persisting symptoms between the attacks. (Thus patients who had symptoms suggestive of bladder outlet obstruction were excluded.) Fifteen patients (30%) presented with a single attack of cystitis and 25 (50%) had had recurrent attacks. Six patients (12%) were referred because of an attack of epididymo-orchitis and 4 (8%) with a history suggestive of upper tract infection (Table 1).

The patients' ages ranged from 18 to 72 and the average age of the group was 47 years; 27 (54%) were aged 50 or less.

On examination at the time of first presentation in the urology clinic, 5 patients had signs of epididymo-orchitis, 3 had flank tenderness and one had a nodular prostate. No relevant clinical abnormalities were found in the remaining patients and digital estimations of prostatic size have not been recorded herein since they were often inaccurate and not necessarily of urodynamic significance.

Routine urine bacteriology confirmed the presence of infection in 37 patients, but 13 had already received antibiotics and their urine was either normal or contained only white cells. They have been included as their referral letters indicated the organisms cultured from their pre-treatment urine samples (Table 2).

The patients were then investigated by performing a conventional intravenous urogram followed by urodynamic pressure/flow videocystography (Bates *et al.*, 1970; Bates and Corney, 1971). The investigations were not done in the presence of untreated infection.

Results

The results of bacteriological culture of urine are given in Table 2. Coliform organisms were responsible for the infection in 42 cases (84%). *Myco. tuberculosis* was cultured from the urine of one

Table 1 Presenting History in 50 Males With Urinary Tract Infections

A single attack of cystitis	15
Recurrent attacks of cystitis	25
Epididymo-orchitis	6
Upper tract infection	4
Total	50

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Table 2 Infecting Organism in 50 Males With Urinary Tract Infections

Coliform species	42 patients
Staph. pyogenes	2 patients
Proteus spp.	2 patients
Str. faecalis	2 patients
Pseudomonas	1 patient
Klebsiella	1 patient
Staph. albus	1 patient
Myco. tuberculosis	1 patient
Total	52 patients

Two patients had infections with 2 organisms.

patient presenting with epididymo-orchitis but no other urinary symptoms.

Intravenous urography revealed unequivocal abnormalities in 11 patients (Table 3). The size of the prostate that appears as a prostatic impression on the base of the bladder is not necessarily of urodynamic significance and the presence of post-micturition residual urine after a conventional intravenous urogram has also not been included in this table for reasons to be discussed later, especially in relation to the findings on videocystography.

The results of pressure/flow videocystography are given in Table 3. For the investigation to be regarded as "normal", the bladder must have a capacity of less than 800 ml with a cystometrogram showing no signs of detrusor instability on provocative testing and the ability to void to completion at a flow greater than 17 ml/s with a detrusor pressure below 60 cmH_2O, and with no signs of ureteric reflux. Only 10 of the 50 patients had bladder functions fulfilling these criteria.

Outflow Obstruction—25 Patients (50%)

Twenty-five patients had dynamic outflow obstruction; of these 15 had unequivocal obstruction at the bladder neck level only, whereas 10 patients had prostatic obstruction; 4 more had both bladder neck and prostatic urethral obstruction.

No Outflow Obstruction—25 Patients (50%)

Apart from the 10 normal cases, 7 patients had detrusor instability with no signs of outflow obstruction. One of these patients had diabetes mellitus and another had bilateral ureteric reflux and a large bladder diverticulum. Of the remaining 8 patients with stable detrusor function, one also had a large bladder diverticulum which contained a residue of 150 ml at the end of micturition. Another patient had bilateral ureteric reflux up to the kidneys and a third patient had unilateral ureteric reflux. Five patients had large bladder capacities: 800 ml in 2 and 900 ml in 3 patients. However, their bladders looked normal and they all voided with normal pressure and flow recordings and had no signs of outflow obstruction, but one patient had a large volume of residual urine in the bladder after micturition because of premature detrusor decompensation.

Discussion

In this series pressure/flow videocystography revealed abnormalities in 40 (80%) of the patients investigated compared with only 11 (22%) found by conventional intravenous urography, which cannot be relied upon to detect lower urinary tract

Table 3 Intravenous Urography and Videocystography: Findings in 50 Males with Urinary Tract Infections

Intravenous urography		*Videocystography*	
Bladder trabeculation	2	*Obstructed*—50%	
Bladder diverticula	2*	Bladder neck obstruction	15
Bladder calculus	1	Prostatic obstruction	6
Prostatic calculi	1	Bladder neck + prostatic obstruction	4
Gross obstructive uropathy	1	*Not obstructed*—30%	
Bilateral hydroureters	1	Idiopathic detrusor instability	6(1*)
Bilateral ureteric reflux (confirmed on video)	1	Neuropathic detrusor instability	1
Unilateral partial duplex kidney and ureter	1	Ureteric reflux	3(1*)
Renal caliceal diverticulum	1*	Bilateral 2	
Congenital absence of kidney	1	Unilateral 1*	
		Idiopathic decompensating bladder + bladder diverticulum	1
		Large capacity bladder	5
		Large bladder diverticulum	1*
12 abnormalities in 11 (22%) patients		43 abnormalities in 40 (80%) patients	
Normal 39 (78%) patients		Normal 10 (20%) patients	

* The same patient.

Table 4 Intravenous Urography and Videocystography: Findings in 50 Females with Urinary Tract Infections

Intravenous urography		*Videocystography*	
Partial duplex kidney and ureter	3	Distal urethral stenosis	6
Unilateral 1		Idiopathic detrusor instability	2
Bilateral 2		Bilateral ureteric reflux	2
Pyelonephritic renal changes	3	Unilateral ureteric reflux	2
Unilateral 1			
Bilateral 2			
Mild pelviureteric junction obstruction	2		
Unilateral 1			
Bilateral 1			
Bilateral ureteric reflux (confirmed on video)	1		
Renal caliceal diverticulum	1		
Congenital absence of kidney	1		
Normal = 39			
11 abnormalities in 11 patients		12 abnormalities in 12 patients	
Normal 39		Normal 38	

or bladder outflow abnormalities. Endoscopic assessment may also be unrewarding or frankly misleading in the diagnosis of urodynamic disorders (Turner-Warwick *et al.*, 1973).

Twenty-seven patients were aged 50 or less and of these 10 had bladder neck obstruction, one of whom had combined bladder neck and prostatic urethral obstruction; *i.e.* 37% of our patients aged 50 or less had outflow obstruction at the level of the bladder neck. Of the 23 cases aged over 50, 6 were obstructed at the bladder neck only, 6 at the level of the prostatic urethra, and 3 had combined bladder neck and prostatic outflow obstruction. The relatively small number of cases of prostatic obstruction in this series occurs because the majority of such cases already had symptoms of obstruction at the time of first presentation, which excluded them from the series. By contrast, patients with bladder neck obstruction rarely complain or even notice that they have a "non-competitive" stream, since the underlying condition is probably life-long and they have never known anything better.

Seven patients had detrusor instability with no evidence of outflow obstruction. After excluding the diabetic and the patient in whom there was co-existing ureteric reflux and a bladder diverticulum, it is difficult to explain any relationship between detrusor instability and urinary tract infection in these cases, especially as the infections had been treated before videocystography was performed.

Five patients had large capacity bladders as defined by Weir and Jaques (1974). All of them voided with normal pressures and flow rates and without signs of outflow obstruction, but one patient had a large volume of post-micturition residual urine in his bladder at the end of videocystography and it may be that some of these people do not always void to completion and may often carry a residual urine.

In this department we do not consider the finding of post-micturition residual urine at the end of a conventional intravenous urogram to be necessarily a significant sign of outflow obstruction. During a conventional intravenous urogram the patient should void immediately before the examination commences and again 20 to 30 min later. Within this short period his bladder may not have filled sufficiently for him either to want or even to be able to void normally, since a bladder must contain at least 250 ml before it attains its full voiding potential (Rollema *et al.*, 1977). This problem can be overcome by waiting until the patient feels his bladder is full again. He can then void into a flow meter (which helps in the assessment of outflow obstruction) and only then have a post-micturition film taken; any residual urine left will be highly significant. We call this modification of a standard intravenous urogram an intravenous urodynamogram (Turner-Warwick *et al.*, 1979). For example, in this series 8 patients had residual urine present at the end of conventional intravenous urography, but the residue was present in only 4 of these 8 patients when they underwent videocystography. The percentage of male patients in this series with abnormalities detected by videocystography (80%) suggests that all males presenting with unheralded urinary tract infections alone require a full urodynamic evaluation. Even a single attack of cystitis warrants this attention, since 11 of the 15 patients presenting in this way had abnormalities on videocystography. By contrast, urinary tract infections in females are common and not often associated with an underlying structural or functional abnormality; indeed in asymptomatic females significant bacteriuria may occur in up to 2% of young women and 15% of post-menopausal women (Kass, 1962). This is not surprising, since the female urethra may be colonised by bacteria as high as the bladder neck (Cox, 1966).

Investigation of a similar but unmatched series of 50 female patients with recurrent infections referred from our urology clinic for urodynamic evaluation revealed that the percentage of upper tract abnormalities was the same as in the men, but lower urinary tract abnormalities were much fewer—24% as against 80% respectively (Table 4). In females with urinary tract infections videocystography may be reserved for the diagnosis of suspected cases of actual or relative outflow obstruction which have been suggested by the findings of a poor flow rate and post-micturition residual urine on a screening intravenous urodynamogram.

We conclude that investigation of male patients with unheralded urinary tract infections by the standard urological techniques of intravenous urography and endoscopy is inadequate. Appropriate urodynamic evaluation is essential. The majority of these male patients have a significant underlying urodynamic abnormality which requires urodynamic investigation, whereas the chances of finding remediable underlying urodynamic abnormalities in females with recurrent urinary tract infections are small.

One urodynamic screening test is the intravenous urodynamogram. This alone may indicate the underlying diagnosis, whilst pressure/flow videocystography can be reserved for more complex cases and use in a specialist urodynamic unit.

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An Evaluation of the HCG Stimulation Test in the Investigation of Male Infertility

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Summary—Of 159 patients being investigated at the infertility clinic during 1978, 31 agreed to undergo the human chorionic gonadotrophin (HCG) stimulation test. Twenty-one of these patients exhibited varying degrees of oligozoospermia and their response to HCG, measured by a rise in serum testosterone, was not significantly different from that of the remaining patients who had normal sperm counts.

Endocrine function of the testes appears to be unaltered even in patients with severely impaired tubular function. It is concluded that assessment of Leydig cell function is of no value in the routine investigation of male fertility.

The development of specific and highly sensitive radio immunoassays for gonadotrophin and testicular steroids has ensured that in most centres endocrinological assessment can be readily carried out during investigation of the subfertile male; this entails the measurement of follicle-stimulating hormone (FSH), luteinising hormone (LH), testosterone and prolactin in the serum.

However, the demonstration that gonadotrophins and testosterone are secreted throughout the day in a pulsatile manner (Naftolin *et al.*, 1973; Baker *et al.*, 1975) suggests that isolated estimations of these hormones may not represent their true levels. Thus, although several measurements of serum testosterone may provide a guide to Leydig cell capacity, De Kretser *et al.* (1974) stated that complete characterisation of this particular aspect of testicular function may be obtained only by the use of a dynamic test such as stimulation with human chorionic gonadotrophin. Using this test, he subsequently showed that patients with defective seminiferous tubular function frequently demonstrated an impaired Leydig cell response.

This study was carried out to establish whether the HCG stimulation test has a place in the routine investigation of male fertility. This involved the analysis of:

1. The testosterone response to HCG in normal men and groups of men with varying degrees of oligozoospermia.
2. The relationship between the testosterone response and the baseline serum testosterone.

Materials and Methods

The HCG test was performed on 31 subjects selected at random from 159 patients who attended the infertility clinic of the Royal Victoria Hospital, Belfast, during 1978. There were 10 patients with an average sperm count greater than 40 million/ml and motility of at least 60%; these constituted the normal group. The remaining patients were divided into 2 groups: 13 with sperm counts less than 20 million/ml and 8 with azoospermia. Cases of obstructive azoospermia were excluded from this study by using only azoospermic patients with a significantly elevated serum FSH level. All subjects had at least 3 semen analyses carried out, each of which followed 3 days' abstinence from sexual intercourse. No patient had received any hormonal treatment related to his infertility over the previous 6 months.

The HCG stimulation test involved giving the patient 1500 iu HCG (Pregnyl; Organon) intramuscularly on days 1 and 3, and serum samples were taken on days 1, 3, 4 and 12 for estimation of testosterone. The blood sampling was performed at approximately the same time each day to avoid variation resulting from diurnal rhythm.

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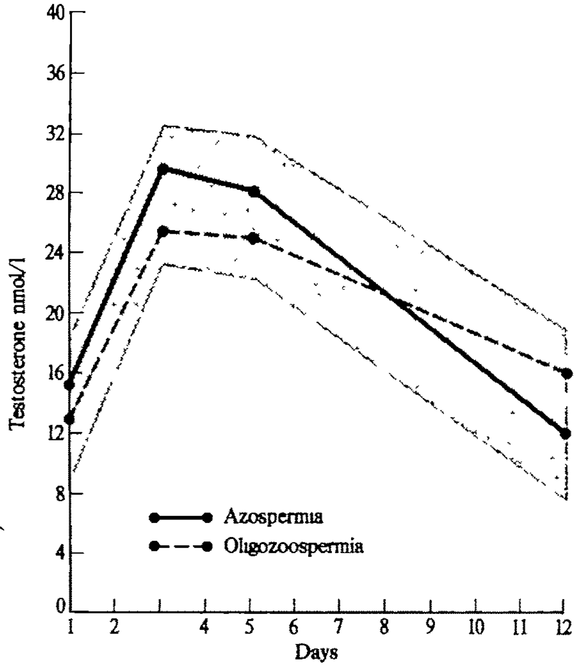

Fig. Serum testosterone following HCG stimulation. The shaded area represents the response, ±2 SDs, in the normal group.

Results

In the Figure the shaded area represents the mean testosterone response ± 2 SDs in the normal group. The mean responses in the 2 other groups clearly lie within this range. All patients produced a marked rise in serum testosterone following the initial injection of HCG; the maximum level was recorded on day 5 in 12 cases, while in the remainder there was no further rise after day 3. In every case the serum testosterone level had returned to within the normal basal range by day 12.

The Table shows a detailed analysis of the data from each group. There is no significant difference in the mean basal testosterone levels in the 3 groups; furthermore, there is no significant difference in the maximum testosterone response or the mean percentage rise. Also, no correlation was found in any group between baseline serum testosterone and the testosterone response.

Table Testosterone Levels Before and After HCG Stimulation Test Related to Degree of Sperm Output

	Normal $>40 \times 10^6$/*ml* (*n = 10*)	$<20 \times 10^6$/*ml* (*n = 13*)	*Azoospermia* (*n = 8*)
Mean basal testosterone (nmol/l)	15.2	13.1	16.45
Range	9.8-18.4	5.0-19.6	6.4-20.0
Mean max. testosterone (nmol/l)	28.3	25.3	29.4
Range	24.0-36.1	15.1-28.0	14.4-41.0
Mean rise (%)	86.2	93.0	82.1

Discussion

To establish that the assessment of the capacity of Leydig cells to secrete testosterone is relevant in the routine evaluation of male fertility it would be necessary to demonstrate an obvious difference in the testosterone response between groups of patients with widely differing sperm output. The results obtained in this study, however, show no significant difference between such groups, Leydig cell function apparently remaining within normal limits not only in patients with moderate oligozoospermia but even in those with tubular defects severe enough to produce azoospermia. This finding, substantiating other reports (Masala *et al.*, 1979; Ruder *et al.*, 1974), is in distinct contrast to the claim that there is an impaired response to HCG in oligozoospermic males (De Kretser *et al.*, 1975). Since it is generally accepted that there is no correlation between basal serum testosterone and the sperm count (Rosen and Weintraub, 1972; Franchimont *et al.*, 1972; Lawerence and Swyer, 1974), one might logically expect such a uniform response to HCG stimulation from these groups. Also, the absence of correlation between the initial testosterone level and the maximum level obtained confirms our original premise that isolated readings of this hormone level are not representative of the Leydig cell reserve.

The HCG stimulation test produced a similar testosterone response in patients exhibiting all degrees of impaired spermatogenesis and therefore has no place in the routine investigation of the subfertile male. Its value in establishing the presence of testicular tissue, *e.g.* in cases of cryptorchidism and in certain sex chromosomal abnormalities, is unquestioned.

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Case Reports

Capillary Haemangioma of Male Urethra

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A 30-year-old male, who was a known case of bronchiectasis, had 2 episodes of urethral bleeding over a period of 2 months. Physical examination showed a small, pinkish polypoidal lesion protruding through the external urethral meatus.

Excretory urography, an ascending urethrocystogram and cystourethroscopy were unremarkable. A wide excision of the lesion with meatoplasty was carried out. Microscopic examination showed a polypoidal lesion covered with squamous epithelium and composed of multiple small capillary channels (Fig.).

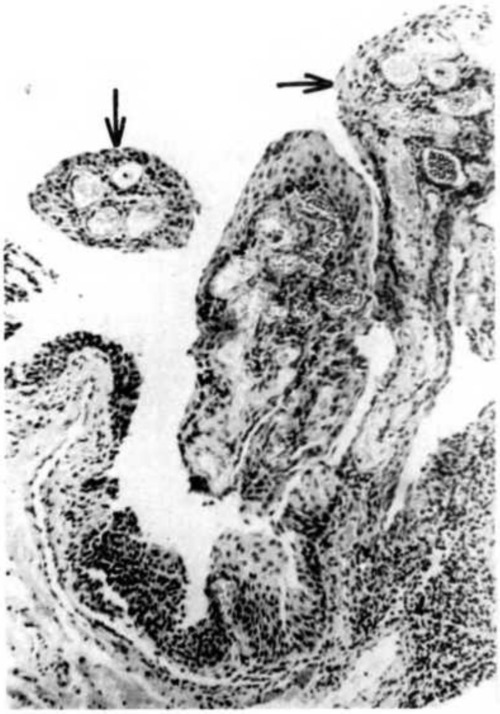

Fig. A polypoidal lesion composed of multiple capillary channels (arrows). The lesion is covered with squamous epithelium (H and E ×44).

Comment

Urethral haemangiomas are very rare. They can occur in any age group, the majority being in the third decade (McCrea, 1948; Tilak, 1967). The lesion may be either solitary and papillary or an extensive sessile growth. Morphologically benign, they often recur and should be treated by wide excision (Manuel *et al.*, 1977). Our patient remains well 2 years after surgery.

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Three Polypoid Colorectal Tumours Associated with Different Types of Ureterocolic Implantation

N. O'HIGGINS, J. DIGNEY, F. A. DUFF and D. G. KELLY, *Department of Surgery, St Vincent's Hospital and University College, Dublin, Eire*

The development of 3 polypoid lesions, 2 of them adenocarcinomas, at the site of previous ureterorectal implantations in a 29-year-old man with *ectopia vesicae* is described.

Case Report

A male patient underwent bilateral ureterocolic anastomosis for exstrophy of the bladder in 1951 at the age of 2 years. A Coffey type anastomosis was carried out, the left ureter being implanted more proximally than the right into the bowel. He was well for 15 years, when he developed a stricture at the lower end of the left ureter; this was treated in 1966 by implantation of the ureter into the sigmoid colon at a higher level, employing a mucosa-to-mucosa suture. In February 1971 he was found to have hydroureter and hydronephrosis on the right side and a right ureterosigmoidostomy was carried out. At operation an intraluminal mucosal nipple was made. In July 1971 an ileal conduit was fashioned.

In June 1978 he presented with rectal bleeding. At colonoscopy a polypoid, poorly differentiated adenocarcinoma was found at the rectosigmoid junction. At operation 2 ureteric remnants were traced to the sigmoid colon and the polypoid tumour was found to be situated at the point of entry of the proximal ureteric stump (Fig. 1). The sigmoid colon was resected and histology demonstrated a poorly differentiated adenocarcinoma which had invaded the stalk of the polyp and had spread to the mesocolic lymph nodes. He remained well for 3 months but then developed further rectal bleeding. At colonoscopy a tumour was seen 20 cm from the anal margin. Re-exploration was carried out on 5.2.79. Two polypoid lesions were palpable in the rectum. An extended left hemicolectomy was carried out, the transverse colon being anastomosed to the mid-rectum. The 2 polypoid lesions measured 4 × 2 × 2 cm and 4 × 4 × 4 cm (Fig. 2). The proximal polyp was found to consist of regular mucus secreting glands and running into this lesion was a tubular structure, lined by transitional epithelium, suggesting a ureteric remnant. Microscopy of the lower polyp showed it to be a poorly differentiated mucus secreting adenocarcinoma. The lymph nodes in the area were not involved by tumour. He was well for 4 months but died 6 months after operation from hepatic metastases.

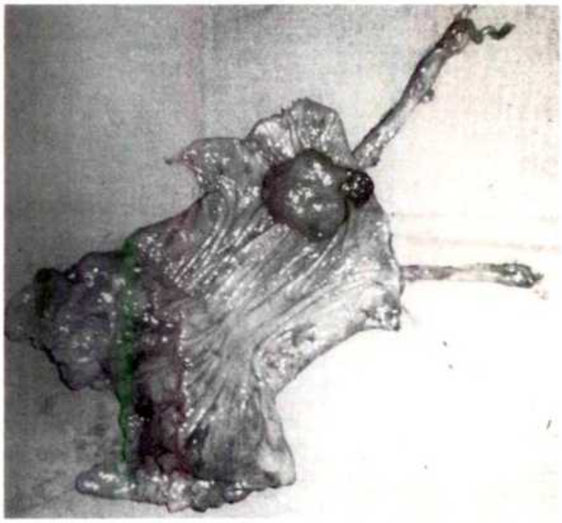

Fig. 1. Polypoid adenocarcinoma at point of entry of proximal ureteric remnant into the colon. No abnormality was found histologically at the lower ureteric orifice.

Comment

Neoplasia at the site of ureterocolic anastomosis has been described frequently (Whitaker *et al.*, 1971; Carswell *et al.*, 1976; Mogg, 1977; Parsons *et al.*, 1977; Sooriyaarachchi *et al.*, 1977; Narayana *et al.*, 1978). In our patient there was a latent period of 12 years before the sigmoid lesion was identified and 28 years before diagnosis of the rectal lesions. Having had both ureters implanted into the rectum and later reimplanted into the sigmoid colon before the ileal conduit was fashioned, he therefore had 4 areas in the large intestine which were at risk of developing polypoid lesions. He developed such tumours at 3 of these 4 sites, a situation not recorded previously. Two of these lesions were poorly differentiated adenocarcinomas. The relationship between polypoid colonic lesions, benign or malignant, at the site of ureterosigmoidostomies is most unlikely to be fortuitous because (*a*) the age at presentation is much younger than colorectal tumours developing in the general population and (*b*) the incidence of polypoid tumours is between 100 and 550 times greater in patients who have had ureterocolic anastomoses than in the general population (*National Cancer Surgery Study*, 1975; Parsons *et al.*, 1977; Sooriyaarachchi *et al.*, 1977). The fact that our patient, with an otherwise normal colon, developed 3 lesions, 2 of them malignant, in direct proximity to ureteric implants, makes the evidence extremely strong that a causal relationship exists.

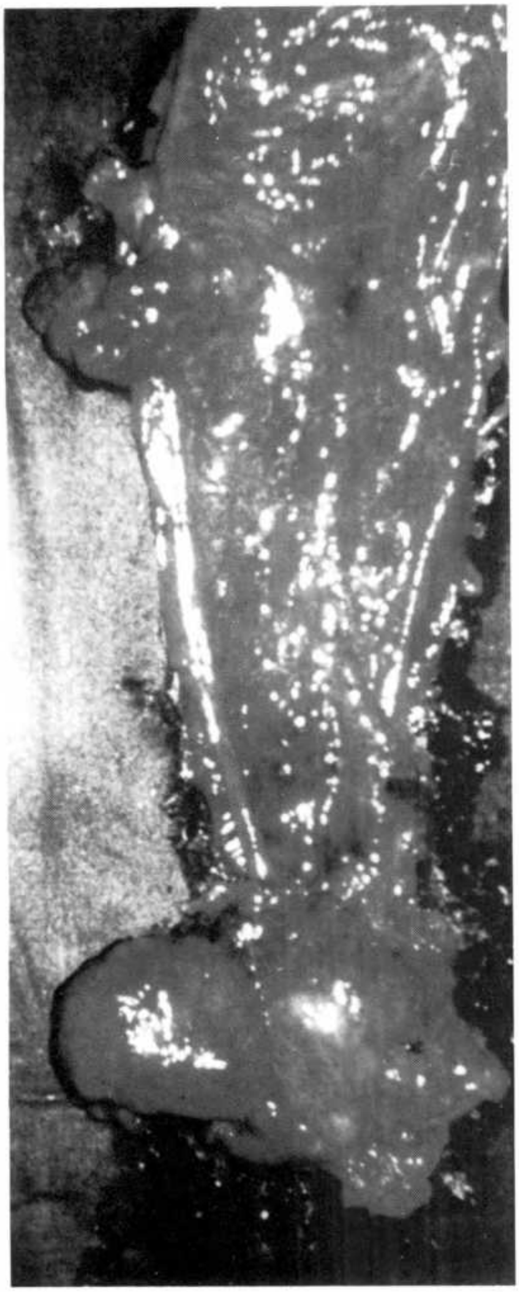

Fig. 2. Specimen of colonic resection demonstrating 2 polypoid lesions at the site of previous ureteric implants. The proximal lesion was a benign polyp, while the lower tumour was a poorly differentiated mucus secreting adenocarcinoma.

There has been a suggestion (Mogg, 1977) that the type of ureterocolic anastomosis fashioned is important in the genesis of colonic cancer. The patient reported here had 3 different types of implant at different times, indicative of changing techniques in this type of surgery. A Coffey implant, a mucosa-mucosal apposition and an intraluminal nipple type of stoma were all carried out. A malignant tumour developed in association with the Coffey implant and with the mucosa-mucosal reconstruction, while a benign polyp formed in relation to the intraluminal nipple. It is likely, therefore, that neoplastic processes with ureterocolic implants can develop irrespective of how the anastomosis is fashioned. It is also noteworthy that all of the lesions came to clinical diagnosis several years after the urine had been diverted to an ileal conduit. Whether the tumours started before the urinary stream had been diverted from the colon or whether the stimulus to the development of neoplasia continued after urinary diversion from the colorectal area to the ileal conduit remains unclear.

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Bilateral Retroperitoneal Xanthogranuloma

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Retroperitoneal processes involving the urinary tract are relatively infrequent and include mainly idiopathic retroperitoneal fibrosis or carcinomatous periureteritis. The existence of a retroperitoneal xanthogranuloma leading to bilateral hydronephrosis is exceptional, since only one case has been reported (Sadoughi *et al.*, 1973).

Case Report

A 59-year-old man was admitted in June 1975 with complete anuria. He complained of left lumbar pain of 4 months' duration but had remained in generally good health. Intravenous urography 2 months previously demonstrated very poor opacification of the left kidney with caliceal dilatation. On admission, serum creatinine was 11.4 mg% and blood urea 126 mg%. Retrograde pyelography showed bilateral hydronephrosis with narrowing of both lumbar ureters.

A right nephrostomy was done with ureterolysis down to the pelvic brim because retroperitoneal fibrosis was suspected. Recovery was uneventful and the nephrostomy tube was removed after one month. Post-operative therapy included 30 mg prednisone bd. Four months later, an excretory urogram disclosed no stasis on the right side and a regression of the left hydronephrosis. The patient was readmitted in December 1975, suffering from left lumbar pain and persistent urinary infection. Intravenous urography showed no excretion on the left side. A left nephrectomy was performed. At operation, the retroperitoneum was extensively infiltrated by a thick fibrous yellowish tissue. Microscopic examination of the excised perirenal tissues revealed a retroperitoneal xanthogranuloma without signs of malignancy (Fig.).

The patient was treated with decreasing doses of corticoids. Four years after the first operation, the treatment was stopped and the patient was doing well. Excretion urography showed a normal right collecting system excepted for a median displacement of the ureter.

Comments

Thirty-two cases of retroperitoneal xanthogranuloma have been reported since the first description by Oberling in 1935 (Arvis *et al.*, 1975). This type of tumour, with characteristics of xanthoma and granuloma, is probably related to "histiocytosis X", a group of illnesses including Hand-Schüller-Christian disease, eosinophilic granuloma and Letterer-Siwe disease. It usually consists of a solitary benign tumour, but infiltration into adjacent organs or metastases may be rarely encountered.

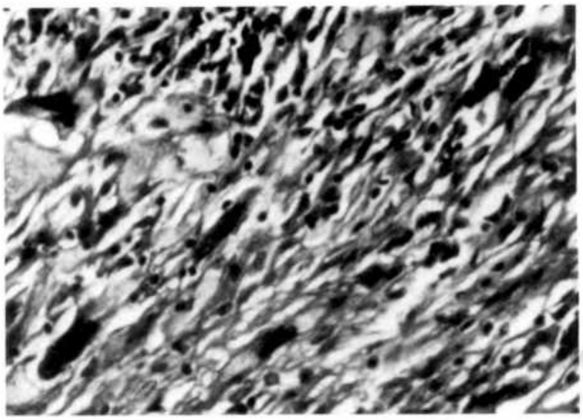

Fig. Xanthogranulomatous tissue containing multiple giant cells of the "Touton" type (H and E ×360).

In the present case, the retroperitoneal invasion by the tumour was bilateral and such a condition is exceptional.

Different treatments for retroperitoneal xanthogranuloma have been used including local excision of the mass, intraperitoneal transposition of the ureter and radiation therapy. The most adequate treatment is impossible to determine because of the dearth of reported cases and insufficient follow-up data. In our case, as retroperitoneal fibrosis was suspected, the patient was treated by corticoïds with encouraging results: transitory regression of the left ureteric obstruction and lack of recurrence on the right side were observed. It is suggested that corticotherapy should be considered as additional treatment of retroperitoneal xanthogranuloma.

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Contrast Filling of Cysts in Potter Type III Adult Polycystic Kidney Disease by Retrograde Pyelography

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Contrast filling of cystic structures during retrograde pyelography has been seen in patients with traumatically ruptured cysts (Reiss, 1967), necrotic abscesses and tumours (Kyaw, 1973). Cyst filling in adult polycystic kidney disease has not been reported previously.

Case Reports

Case 1. S.H., a 45-year-old man, had a family history of kidney failure. His renal function had been declining during the year preceding admission. He underwent excretory urography, and the results were compatible with adult polycystic kidney disease. No contrast material appeared in the cysts. However, during retrograde pyelography some of the cysts were opacified (Fig. 1). On the basis of this finding and the family and clinical history, adult polycystic disease was diagnosed. The patient eventually underwent bilateral nephrectomy and renal transplantation. Pathology examination of the renal tissue confirmed the clinical diagnosis.

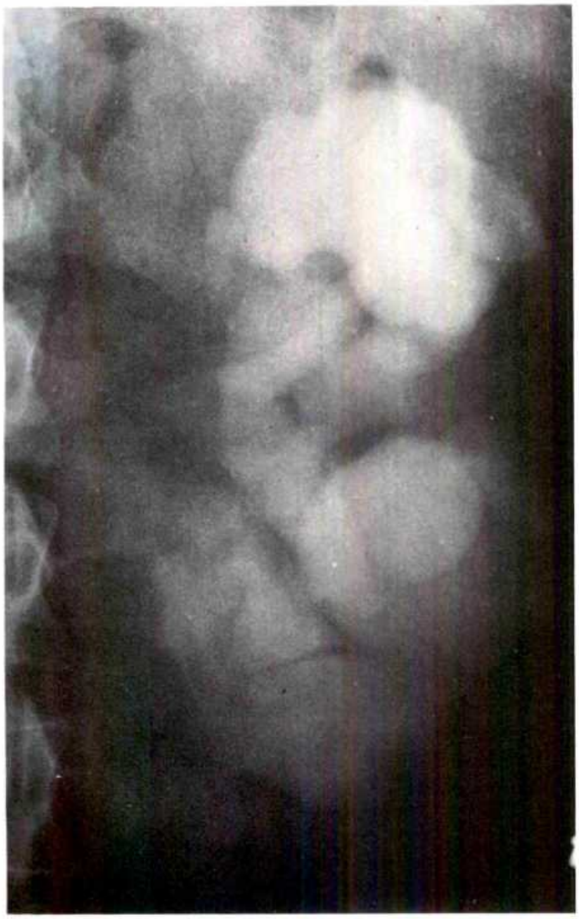

Fig. 1

Case 2. E.B., a 50-year-old man, had a strong family history of adult polycystic kidney disease. He first presented in 1948 with progressive renal failure and hypertension, and polycystic kidney disease was diagnosed. In June 1971, the patient presented with haematuria and he was evaluated to exclude causes for this other than the known disease. The results of excretory urography were compatible with the original diagnosis and no contrast filling of the cysts occurred. During retrograde pyelography some of the cysts filled with contrast material (Fig. 2). The patient's renal failure is being managed medically.

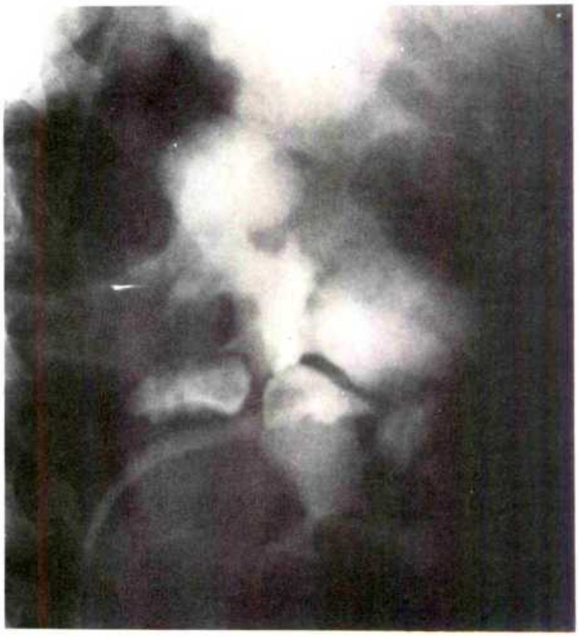

Fig. 2

Comment

In Type III cystic kidneys, each cyst communicates through a tubule with the pyelocaliceal system (Osathanondh and Potter, 1964). Therefore fluid introduced into the pelvis under pressure may fill the cysts. Insufficient pressure probably accounts for the failure of cysts to fill with contrast medium during intravenous urography and the usual retrograde pyelographic examination.

Contrast filling of cysts, when it occurs, may be of diagnostic value. There are several diseases that can, on occasion, mimic the history and the radiographic appearance of polycystic kidney disease. These conditions include multiple renal hamartomas (Wright *et al.*, 1974); bilateral multiple renal adenomas (Meisel, 1954); diffuse, infiltrating kidney disease such as lymphoblastoma (Meisel, 1954) and multiple renal cysts (Hatfield and Pfister, 1972). In these conditions, cystic structures will not be filled during retrograde pyelography.

The other causes of cyst filling can usually be differentiated from polycystic disease without difficulty. In cases in which a simple cyst has ruptured (Reiss, 1967), there will be a history of trauma. A necrotic tumour or abscess may also fill with contrast fluid (Kyaw, 1973) but the cystic structures will have irregular margins.

The appearance of multiple, smooth cystic structures during retrograde pyelography in patients of an appropriate age should be pathognomonic of polycystic kidney disease.

Acknowledgement

We thank Judith Gunn Bronson, MS, for assistance in the preparation of this paper.

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Author's Follow-up

The Place of Prolonged Bladder Distension in the Treatment of Bladder Instability and Other Disorders. A Review after 7 Years

J. C. SMITH, *Department of Urology, Churchill Hospital, Oxford OX3 7LJ*

In 1974 we presented our early results of prolonged bladder distension in the treatment of detrusor instability (Dunn *et al.*, 1974). Higson *et al.* (1978), Ramsden *et al.* (1978) and Higson and Smith (1981) have detailed our further experiences. Using a modification of the procedure described by Helmstein, the bladder is distended to the systolic blood pressure for 4 successive periods each of 30 min. After each distension the bladder is emptied and its capacity measured. An indwelling catheter is left overnight. For repeat distensions (Ramsden *et al.*, 1976) longer periods (usually of 4 and occasionally 6 h) are used or, alternatively, 2 h of continuous distension at systolic blood pressure.

Bladder rupture, which can be treated by catheter drainage, occurred in 5% of patients distended for instability and 15% distended for interstitial cystitis (Higson *et al.*, 1978).

Results

In patients with bladder instability the bladder is distended for about 5 min at systolic blood pressure at the time of cystoscopy. If this markedly improves the symptoms and the instability is confirmed by urodynamic investigation, prolonged bladder distension under epidural anaesthesia is employed. Using this technique, which should always be tried before bladder transection or urinary diversion, about half of the patients will be improved symptomatically one month after distension, although this number falls to 20% at one year and to 10% at 4 years (Higson and Smith, 1981).

In interstitial cystitis prolonged bladder distension has given good results, but patients should be warned of the possibility of bladder rupture which occurs in 15%.

In neuropathic bladder prolonged distension has little effect on the unstable bladder of multiple sclerosis, but may overcome bladder spasm and enable the patient with the indwelling catheter to keep dry. As the urine is usually infected and septicaemia a risk, antibiotics should be given.

It is concluded that prolonged bladder distension has a place in the treatment of severe idiopathic instability that is unresponsive to drugs and it should be tried before major open surgical procedures.

Acknowledgement

I would like to acknowledge that the vast majority of this work was done by my successive research assistants: Michael Dunn, Peter Ramsden, Roger Higson and Timothy Philp.

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Notices

First International Symposium on Minimal Invasive Cancer

Graz, Austria. 1-4 July 1981

Further particulars from: Interconvention, P.O. Box 105, A-1014 Vienna, Austria.

XVth Annual Conference of Urological Society of India

Bombay, India. 25-27 September 1981.

Immediately before the above conference a meeting on "Continuing Education in Urology" will be held from 23-25 September 1981. Delegation fee Rs. 200/- for members and Rs. 250/- for nonmembers.

Further information from: Dr A. Bhajekar, Chief Surgeon, Port Trust Hospital, Antop Hill, Bombay 400 037, India.

International Society for Dynamics of the Upper Urinary Tract (ISDU)

Aarhus, Denmark. 31 August-1 September 1981

Further information from: Professor Dr B. L. R. A. Coolsaet, Department of Urology, Academic Hospital, Utrecht, Catharijnesingel 101, 3500 CG Utrecht, The Netherlands.

C.-E. Alken Prize 1981

An endowment fund under the name of Stiftung C.-E. Alken has been established for the purpose of furthering clinical work and research in the field of urology by presenting an annual award of 10,000 Swiss Francs for the best unpublished work in this field.

The closing date for submission of papers is 1 September 1981 and further particulars may be obtained from Professor E. J. Zingg, Department of Urology, University of Berne, 3008 Berne, Switzerland.

Books Received

Prostaglandins in Cardiovascular and Renal Function. Proceedings of the 20th Annual A. N. Richards Symposium of the Physiological Society of Philadelphia. Edited by A. Scriabine, A. M. Lefer and F. A. Kuehl, Jr. Pp. 498. Lancaster: MTP Press. 1980. Price £29.95.

Acute Renal Failure. Edited by A. Chapman. Pp. 178. Edinburgh: Churchill Livingstone. 1980. Price £15.00.

A Course in Clinical Disorders of the Body Fluids and Electrolytes. G. M. Berlyne. Pp. 240. Oxford: Blackwell. 1980. Price £6.80.

Book Review

Incontinence and its Management. Edited by Dorothy Mandelstam. Pp. 233. London: Croom Helm. 1980. Price £9.95.

Each of the 15 chapters in this book gives an excellent condensation of present knowledge and thinking of the many aspects of urinary and faecal incontinence.

Appropriately, it begins with a detailed consideration of the mechanics of bladder and rectal control and functions and then expands its field into general practice and the community.

The places of drugs, surgery, appliances, nursing methods and psychological management are all considered and clearly and succinctly described.

After reading the first 4 chapters (which include details of urodynamic and rectal dysfunction studies) and then the Glossary (which explains what is meant by the anus, faeces and the urethra), it seemed that this was a book for nobody. But having read the rest of the chapters in some detail, it is certainly a book for everybody.

Miss Mandelstam is to be congratulated on her editing of this book. Perhaps in future editions the page of Notes on Contributors could be displayed less modestly at the front, instead of hidden on page 229, and perhaps the Glossary could be more audience-orientated.

This book is strongly recommended for the whole team of medical and nursing staffs and social workers who have to deal with the challenge of the incontinent adult.

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Experience with omentoplasty. (A. Costantini *et al.*) *Eur. Urol.* 1980, **6**, 265.

Stereoresectoscopy. (U. Jonas.) *Aktuel. Urol.* 1980, **11**, 225.

TECHNICAL DATA

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Presentation The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

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VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contraindications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of VICRYL (Polyglactin 910) and Coated VICRYL Sutures in neural tissue and in cardiovascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Adverse Reactions No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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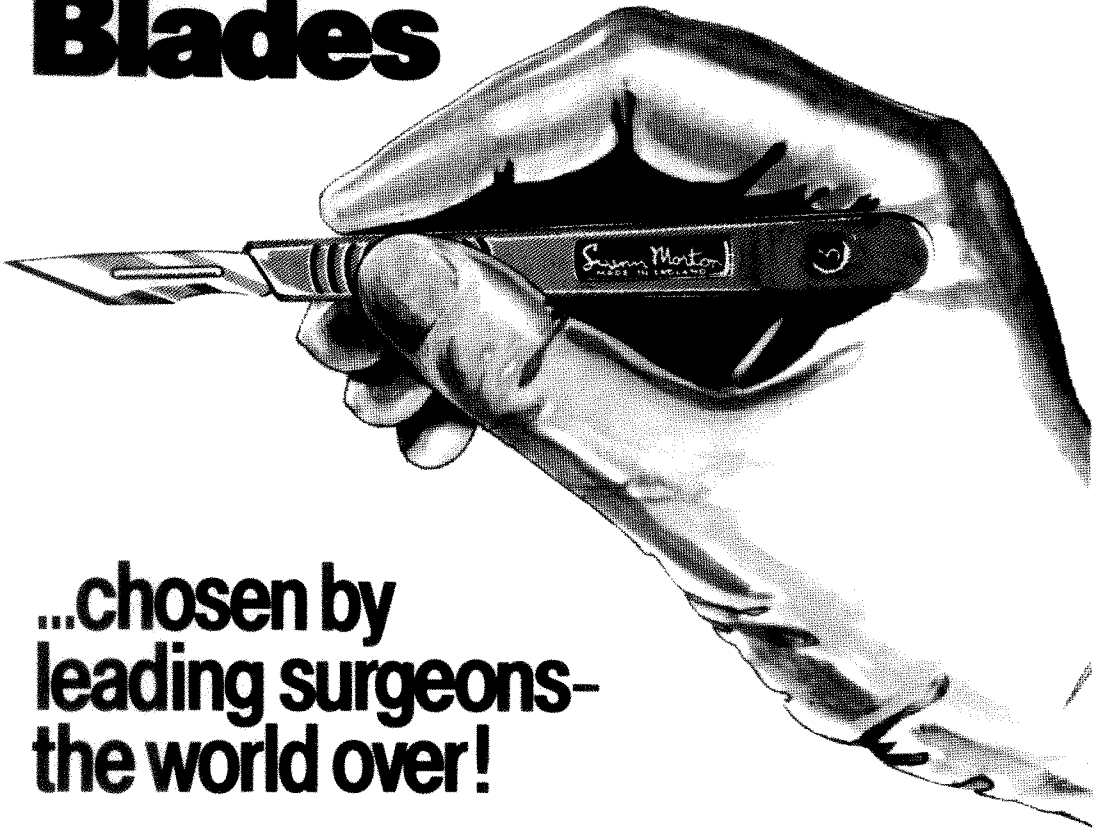

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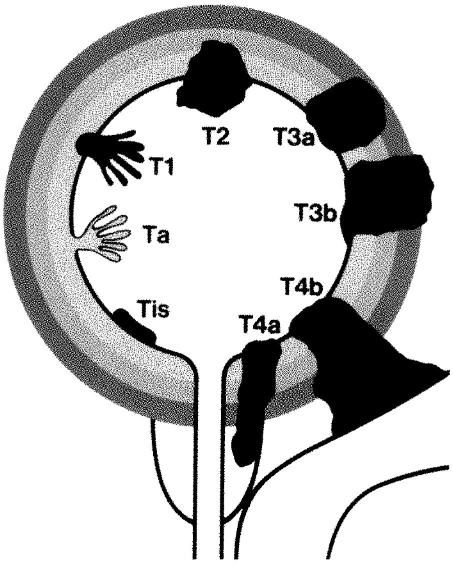

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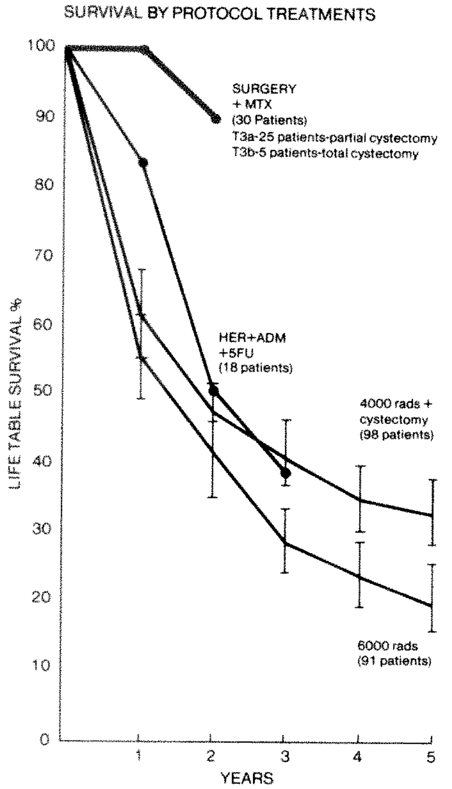

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1. Smith PH. Paper read at *International Symposium on Methotrexate*, London 1979. *Cancer Treatment Reports.* In Press.
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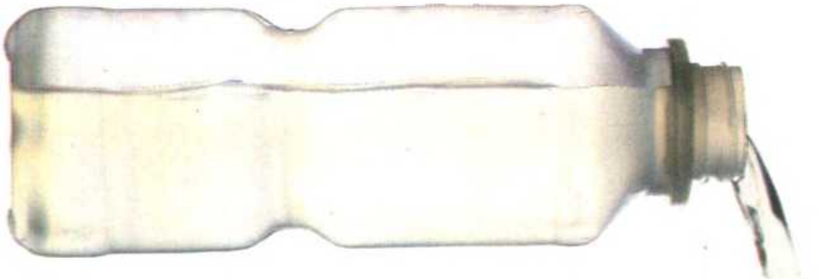

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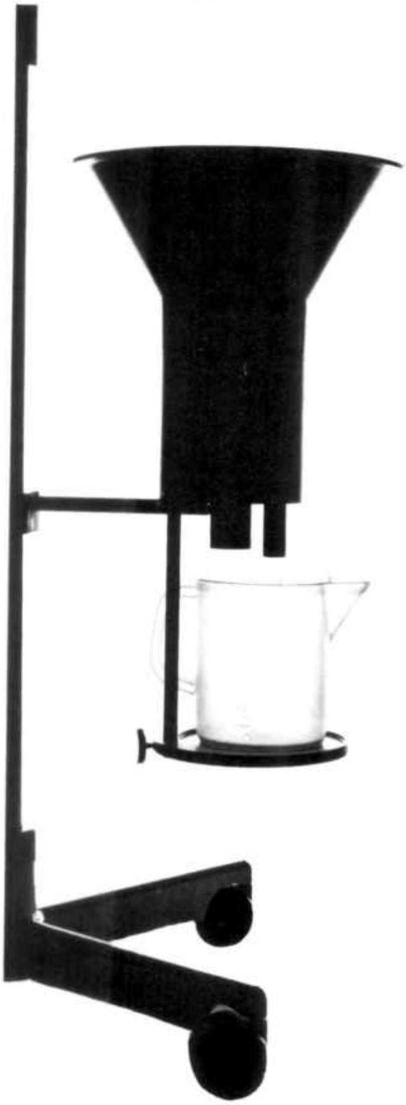

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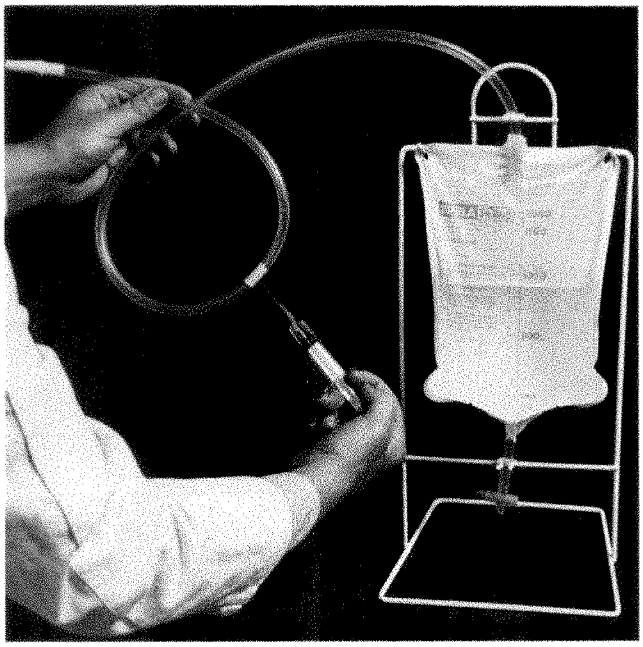

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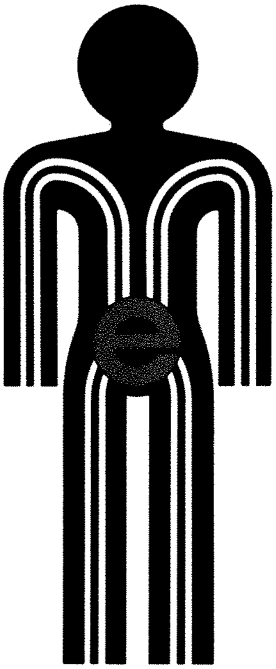

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1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E. J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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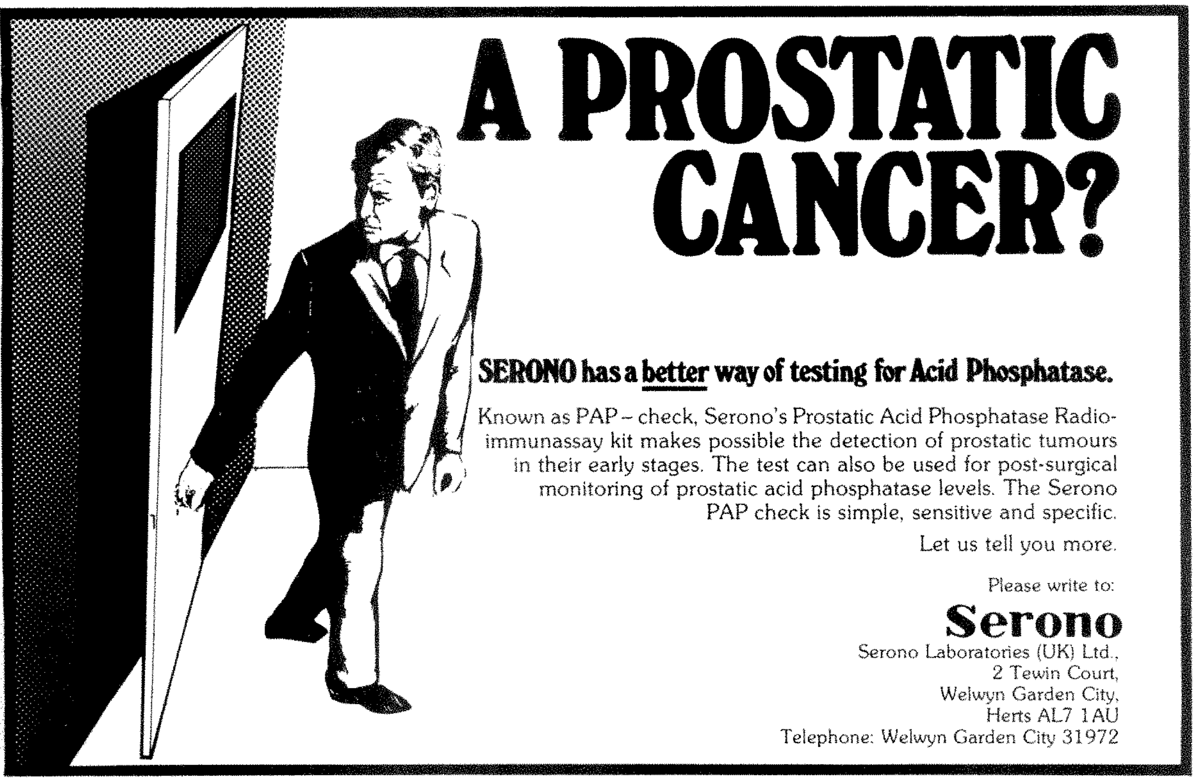

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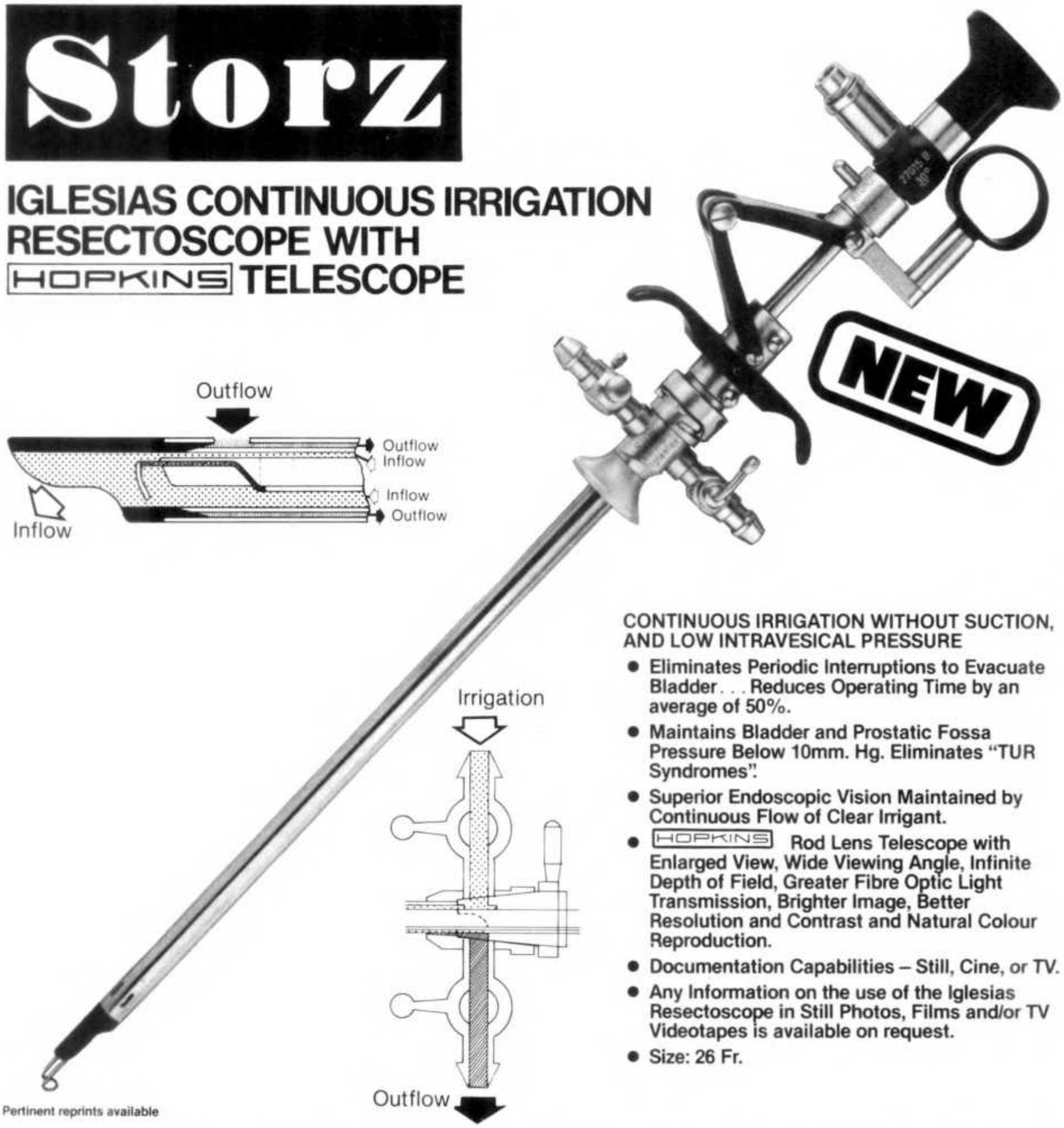

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Hereditary Hypercalciuric Urolithiasis

A Study of a Family

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Departments of Medicine D and Clinical Biochemistry, Tel-Aviv University Medical School, Petah Tikva, Israel

Summary—A family affected with hereditary hypercalciuric urolithiasis is presented. The data suggest that the primary defect is idiopathic hyperabsorptive hypercalciuria, transmitted by an autosomal dominant pattern. This syndrome seems to be common among patients with hypercalciuric urolithiasis.

Investigation of the family of such patients and preventive treatment at the earliest age possible are suggested.

Hypercalciuria is a relatively common aetiological factor in calcium urolithiasis (Hodgkinson and Pyrah, 1958) and may be one of the manifestations of such abnormalities as hyperparathyroidism, renal tubular acidosis, sarcoidosis and malignancies. However, in the majority of cases it is idiopathic (Pak *et al.*, 1974).

In a previous study of 50 male and 24 female patients with idiopathic hypercalciuria associated with urolithiasis we found that 20% had a family history of renal stones (Weinberger *et al.*, 1977) but only one had a family large enough to allow the detailed study which is reported in this paper.

Patients and Methods

M.S., a 52-year-old male Jew born in Turkey, who had suffered from recurrent calcium oxalate urolithiasis since the age of 30, was admitted to our Metabolic Unit. On admission he was asymptomatic. Physical examination and routine haematological and blood chemistry values were all within the normal range. The serum calcium was 2.37 mmol/l and the serum inorganic phosphate 0.9 mmol/l. Routine urine examination was normal, with a morning pH of 5.4 to 6.2. The urinary pattern of amino acids by paper chromatography showed no abnormalities. The urinary 24-h excretion of calcium was, on a diet containing 800 mg of calcium per day, 385 to 425 mg, whereas on a low calcium diet (300-400 mg per day) it was 230 to 260 mg. Tubular reabsorption of phosphate was 85 to 96%. Oral ammonium chloride load test lowered the urinary pH to 4.9. A bone survey showed no abnormalities. Chest X-rays and excretion urography were normal.

Thirty-nine relatives in 3 generations were questioned about a history of renal stone disease and possible cause of hypercalciuria. Two 24-h urine collections were obtained from 13 family members and analysed for calcium and creatinine as described by (Sperling *et al.*, 1974).

Results

The family pedigree is shown in the Figure. Four subjects (all male, one a 6-year-old boy), were found to have hypercalciuric urolithiasis. Two other relatives (one male and one female) were found to have hypercalciuria without urolithiasis, and 4 relatives (2 male and 2 female) were found to have urolithiasis without hypercalciuria (Table). One subject (with recurrent calcium urolithiasis) died of terminal renal failure; we were unable to obtain further information concerning his urinary calcium excretion.

Table Urinary Excretion of Calcium and Inorganic Phosphate in Family Members with Hypercalciuria

Subject	*Sex/age*	*Creatinine*	*Calcium*	*Phosphate*
		mg/24 h		
II- 1	M/52	1530	531	1305
II- 2	M/55	1395	427	1124
III-13	M/32	1526	414	885
III-15	M/30	1620	367	1105
III-17	F/38	1162	385	1331
IV- 1	M/6	590	132	538

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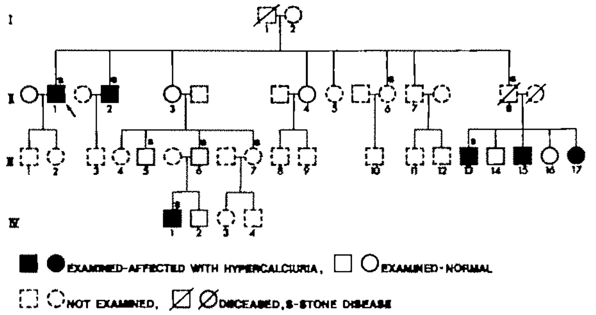
I
II
III
EXAMINED-AFFECTED WITH HYPERCALCIURIA,
EXAMINED-NORMAL
NOT EXAMINED,
DECEASED, S-STONE DISEASE

Fig. Pedigree of affected family.

Discussion

In the family reported, several members spread over 3 generations had either idiopathic hypercalciuria, urolithiasis or both conditions. We believe that all of the subjects affected have the same syndrome, *i.e.* hereditary (idiopathic) hypercalciuric urolithiasis. In this syndrome the idiopathic hypercalciuria is the congenital defect, whereas the urolithiasis is frequently associated with it. Idiopathic hypercalciuria is classified aetiologically into absorptive and non-absorptive types. In the former there are considerable fluctuations in urinary calcium excretion which is normal or high, depending on the dietary calcium intake. The finding that the patient's urinary excretion of calcium decreased markedly when he was on a low calcium diet is compatible with hyperabsorptive hypercalciuria. Furthermore, the finding of 4 relatives with urolithiasis without hypercalciuria is also in accordance with this classification. Two relatives were found to have hypercalciuria without urolithiasis. This finding was not unexpected since the formation of stones depends on many factors other than hypercalciuria, including urine volume and inhibitors.

In view of these findings it is suggested that relatives affected with hypercalciuria alone, with urolithiasis alone or with both, should all be considered as similarly affected. Accordingly, the data on this family are compatible with an autosomal dominant transmission of the defect. Both sexes are affected and there is direct transmission from fathers to both sons and daughters. Consistent with this pattern of transmission, family member II-3 should also have been affected. It is probable that both urine collections were obtained during a relatively low calcium intake.

This dominant autosomal inheritance of hypercalciuric urolithiasis is compatible with the results of Coe *et al.* (1979) in their study of 8 families. The investigation of our series of patients with idiopathic hypercalciuric urolithiasis (Weinberger *et al.*, 1977; Coe *et al.*, 1979) indicates that this congenital defect may be quite common among patients with renal stones. Since young subjects with this defect suffer from urolithiasis, all offspring of patients with this defect should be investigated so that preventive treatment against renal stones can start at the earliest possible age.

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Bilateral Renal Carcinoma

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Summary—Five patients with bilateral renal tumours are discussed with regard to their treatment and prognosis in an attempt to formulate the most effective surgical approach. The clinical history, physical signs, treatment and prognosis are summarised.

Bilateral renal carcinoma was first reported in 1910 by Chute and occurs in 1.8% of all renal carcinomas (Vermillion *et al.*, 1972).

Opinions vary regarding the treatment of this condition and whilst some authors recommend conservative surgery to preserve some renal function, others suggest bilateral radical nephrectomy with subsequent renal dialysis or transplantation.

The prognosis is variable, but good survival can occur provided that there are no metastases at the time of surgical treatment. It is also important (but often difficult) to differentiate between the simultaneous appearance of primary tumours and the concomitant appearance of secondary tumours which carry a worse prognosis (Wickham, 1975).

Patients

Case 1. E.U., a 55-year-old male, presented with 2 episodes of painless haematuria, weight loss of 6 kg and abdominal pain for 5 months. Physical examination revealed no abnormal signs and the intravenous urogram showed a mass on the lateral border of the right kidney and a "normal" left kidney (Fig. 1). Flush aortography and selective renal angiography showed a right renal carcinoma and a similar small tumour at the lower pole of the left kidney (Fig. 2). The chest X-ray and blood chemistry were within normal limits. He underwent a right radical nephrectomy and a left lower pole partial nephrectomy. Histological examination revealed a renal carcinoma of the right and left kidneys, both involving the renal vein and of similar appearance. He is alive and free of metastases 5 years later with a current blood urea of 9.4 mmol/l and a creatinine of 0.2 mg/dl.

Case 2. J.V., a female aged 57 years, presented with 2 episodes of painless haematuria over 6 weeks. Physical examination revealed no abnormal signs and an intravenous urogram showed a mass in the lower pole of the right kidney; the left kidney looked normal. Flush aortography and selective renal angiography showed a large renal carcinoma of the right kidney and a similar smaller tumour on the lateral border of the left kidney. Chest X-ray and blood chemistry were within normal limits. A right radical nephrectomy was performed and the left kidney biopsied. Histological examination confirmed a right renal carcinoma involving the renal vein and a carcinoma of the left kidney of a different appearance. One week later surgical exploration of the left kidney revealed a central tumour which necessitated removal by radical nephrectomy. She was maintained on renal dialysis for 11 months and then received a cadaver renal transplant. Two-and-a-half years later she is well and free from metastases; her blood urea is 6.4 mmol/l and creatinine is 0.09 mmol/l.

Case 3. E.M., a female aged 52 years, presented with left loin pain and 4 episodes of haematuria over 2 years. Physical examination revealed a palpable tender left kidney and a soft nodular goitre. Intravenous uro-

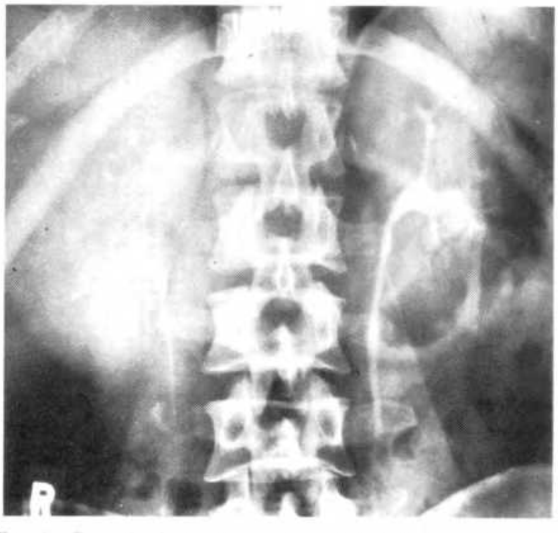

Fig. 1, Case 1 Intravenous urogram showing right renal carcinoma and a "normal" left kidney.

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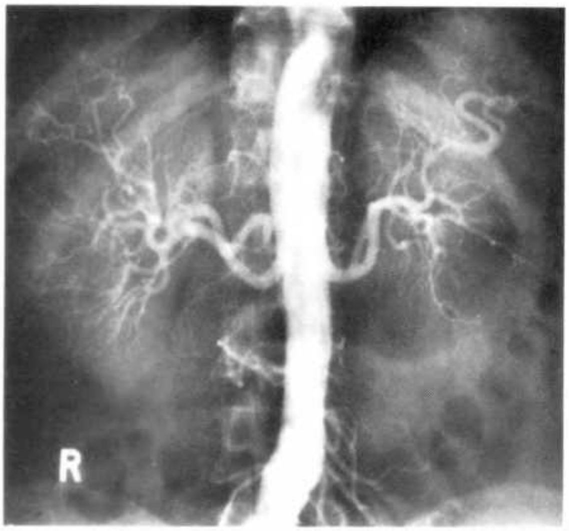

Fig. 2, Case 1 Flush aortogram showing bilateral renal carcinomas.

graphy revealed a mass in the lower pole of the left kidney, whilst the right kidney appeared normal. Flush aortography and selective renal angiography revealed a left lower pole renal carcinoma and a right renal carcinoma in the mid-lateral zone. A left radical nephrectomy and a wedge resection of the right renal tumour were performed. Histological examination revealed a left renal carcinoma invading the renal vein and a well encapsulated right renal carcinoma of similar appearance. She was treated post-operatively with medroxyprogesterone 100 mg tds and was well for 5 years until she developed a mass in the goitre. A subtotal thyroidectomy was performed and histological examination confirmed the presence of a renal carcinoma metastasis within the thyroid tissue. She remains alive but is known to have generalised metastases 8 months after the thyroidectomy. Her current blood urea is 6.8 mmol/l and creatinine is 0.01 mmol/l.

Case 4. D.A., a male aged 44 years, presented with malaise, night sweats, fatigue, weight loss (8 kg) and lumbar discomfort for 1 year. He suffered 2 episodes of right renal colic with haematuria over 2½ years. Physical examination revealed no abnormal signs and an intravenous urogram showed bilateral large kidneys with a mass in the right lower pole (Fig. 3). Flush aortography and selective renal angiography confirmed bilateral renal carcinomas affecting the lower poles (Figs. 4 and 5). Chest X-ray and blood chemistry were within normal limits. A bilateral lower pole partial nephrectomy was performed and histological examination confirmed renal carcinomas, both invading the renal veins and of similar appearance. He remained well for 1 year and then developed general malaise, weight loss and backache. He was found to have a metastasis medial to the left kidney which was treated with radiotherapy (4800 rads locally) and medroxyprogesterone 200 mg tds. He developed further generalised metastases and died 16 months after his initial surgery.

Case 5. G.F., a male aged 48 years, presented with painless haematuria for 9 days and right loin pain for 2 weeks. He had undergone surgical removal of a cerebellar haemangioblastoma 17 years previously and was known to have a recurrent haemangioblastoma of the cerebellum and the lumbar spine which had been treated with radiotherapy. Physical examination revealed bilateral renal masses with ataxia, nystagmus and impaired co-ordination. His chest X-ray was normal, whilst the blood urea was 10.3 mmol/l and creatinine was

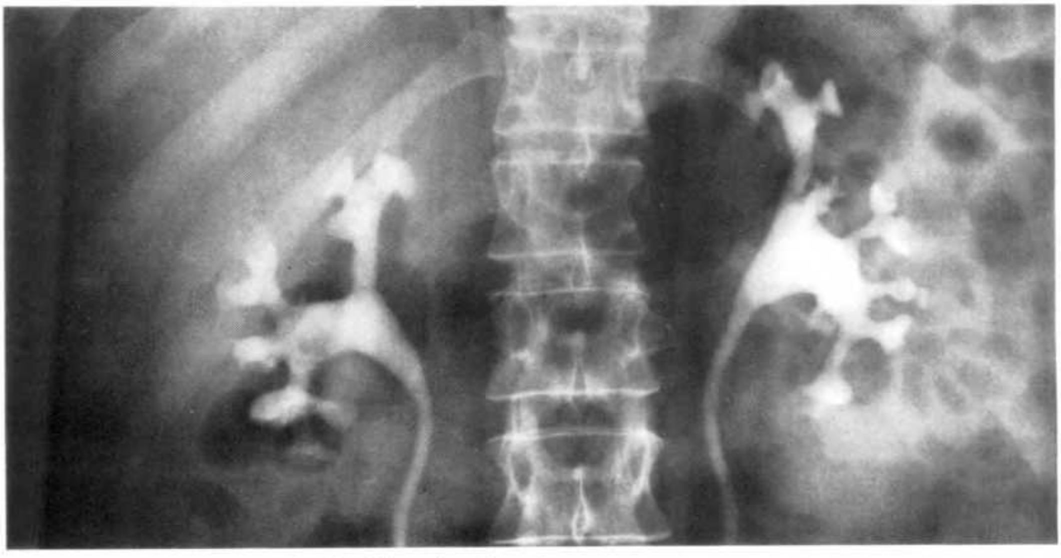

Fig. 3, Case 4 Intravenous urogram showing bilateral renal carcinomas.

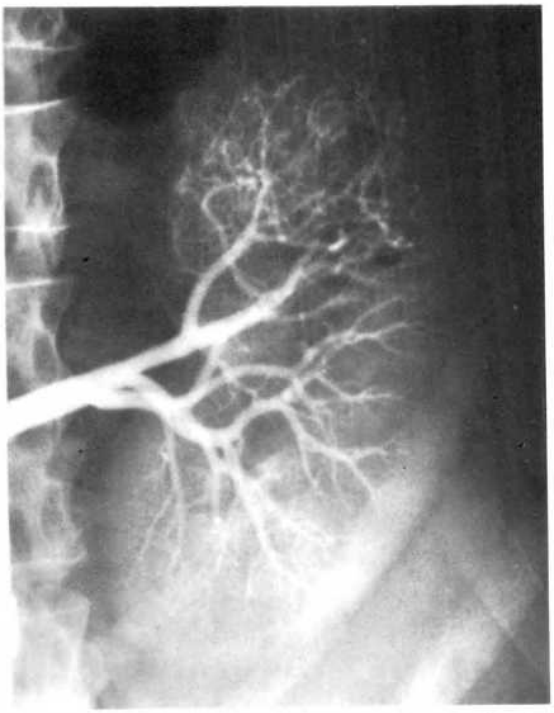

Fig. 4, Case 4 Right selective renal angiogram showing a renal carcinoma.

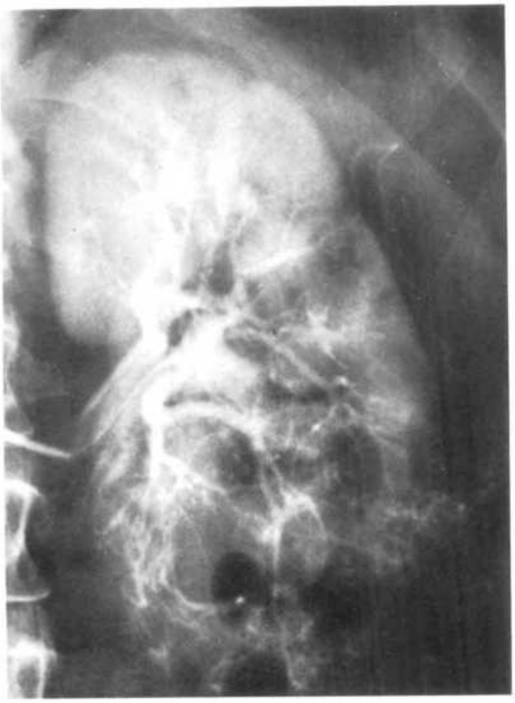

Fig. 5, Case 4 Left selective renal angiogram showing a renal carcinoma.

0.01 mmol/l. An intravenous urogram revealed diffuse bilateral renal masses (Fig. 6) and flush aortography with selective angiography confirmed bilateral renal carcinomas (Figs. 7, 8 and 9).

A diagnosis of Von-Hippel Lindau syndrome was made. A laparotomy revealed bilateral diffuse renal carcinomas with no evidence of metastases; bilateral renal biopsies were performed. Histological examination confirmed renal carcinomas of similar appearance in both kidneys. A bilateral nephrectomy was suggested but he refused surgery. Since his discharge from hospital this patient has undergone a further craniotomy and removal of recurrent cerebellar tumour, but he is alive and his current blood urea and creatinine levels remain within normal limits 6 months after his kidney biopsy.

Discussion

The fate of the first 4 patients is similar to that quoted in the literature (Wickham, 1975). Conservative surgery proved effective in the first and third patients but not in the fourth. Radical surgery was performed on the second patient because it was not possible to preserve any normal

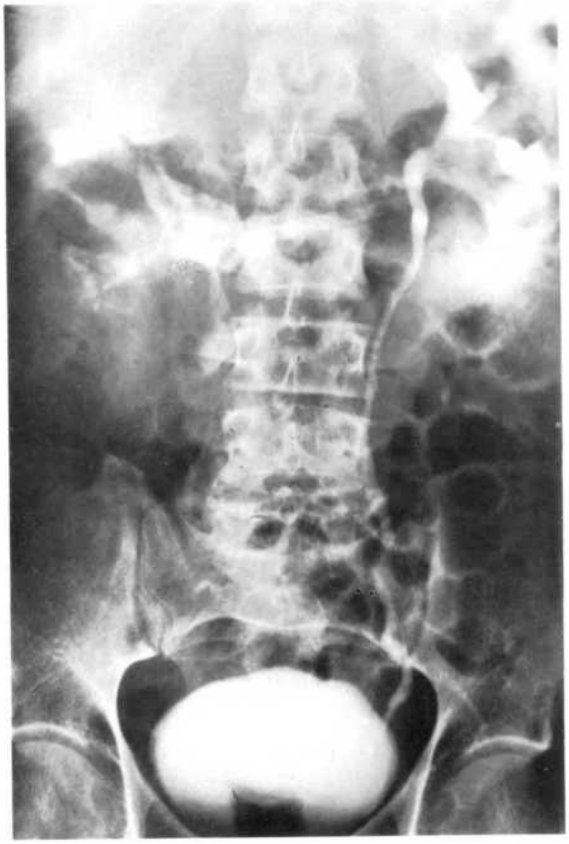

Fig. 6, Case 5 Intravenous urogram showing bilateral renal carcinomas.

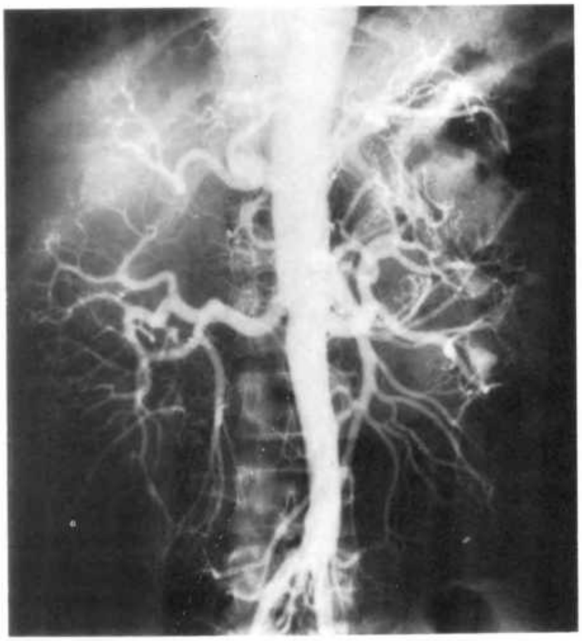

Fig. 7, Case 5 Flush aortogram showing bilateral renal carcinomas.

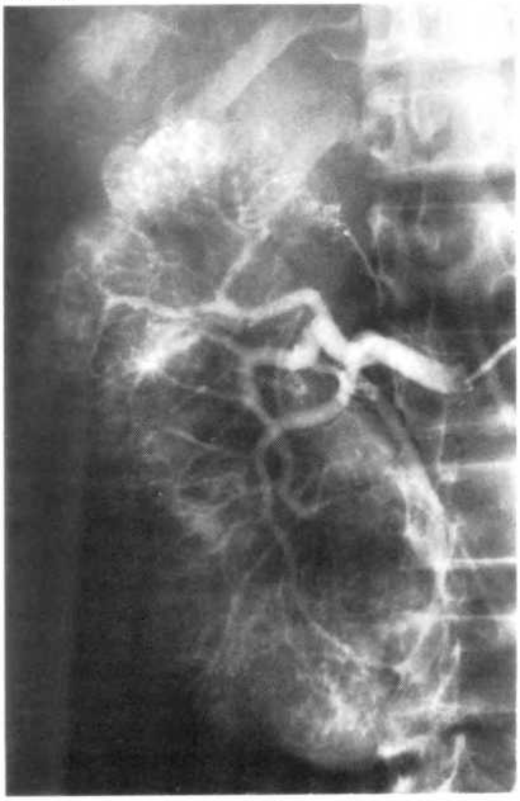

Fig. 8, Case 5 Right selective renal angiogram showing a renal carcinoma.

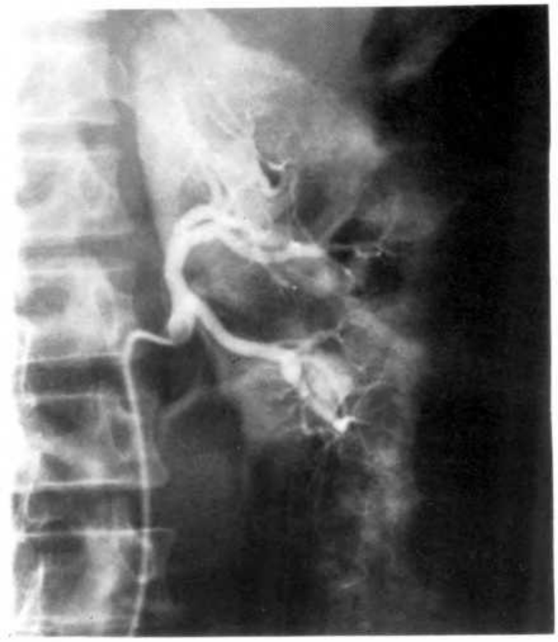

Fig. 9, Case 5 Left selective renal angiogram showing a renal carcinoma.

renal tissue and provide adequate tumour clearance. The fifth patient was offered bilateral radical nephrectomy in view of the multifocal and extensive nature of the tumours, a characteristic of renal tumours in the Von-Hippel Lindau syndrome.

Eighty-one per cent of renal tumours in solitary kidneys occur at the poles (Grabstald and Aviles, 1968) and this means that it is often possible to treat these patients with bilateral partial nephrectomies. The first patient treated in this way was reported by Kolln *et al.* in 1971 and the procedure has the advantage of allowing the patient to exist without the added complications of renal dialysis or transplantation. The disadvantage is the increased risk of incomplete tumour excision and attempts to overcome this problem have lead to the technique of *ex vivo* partial nephrectomy with autotransplantation. This method allows a more detailed dissection with a greater chance of tumour clearance but it is complex, time-consuming and rarely necessary unless there is a large tumour at the hilum (Calne, 1973; Wickham, 1975).

Bilateral nephrectomy is a radical approach to the problem and the patient must then be maintained on renal dialysis. Renal transplantation may be considered if metastases have not appeared one year after nephrectomy.

Stroup *et al.* (1974) reviewed 10 cases of renal carcinoma in solitary kidneys and bilateral renal carcinoma treated by bilateral nephrectomy and renal transplantation. Six patients survived a mean of 28 months. They stated that there was no evidence that immunosuppression promoted tumour growth. Behara *et al.* (1976) maintained that most centres reported a 2-year transplant success rate of 50 to 66% but that less than 8% of patients survived 8 years after transplantation, suggesting that these patients should not receive renal transplants. Puigvert (1976) reported that the 5-year survival rate for bilateral renal carcinoma treated with partial nephrectomy compared with bilateral nephrectomy was identical (23%). Without surgery most patients with bilateral renal carcinoma die within 6 months of diagnosis (Wickham, 1975) but there have been isolated reports of long-term survival without surgical treatment (Johnson *et al.*, 1978).

It is important that a contralateral renal carcinoma is not overlooked during the investigation of a renal mass. Flush aortography and bilateral selective renal angiography are therefore recommended during the investigation of all renal tumours.

The surgical approach should then be planned for the individual patient as the overall survival rates do not vary with the different methods of treatment. Partial nephrectomy is the treatment of choice if adequate tumour clearance can be achieved because the added problems of renal dialysis and transplantation are avoided. Bilateral nephrectomy may be necessary in more extensive tumours and is always indicated in cases of Von-Hippel Lindau syndrome and tuberous sclerosis, which are associated with multifocal bilateral renal tumours (Fetner *et al.*, 1977).

The transperitoneal approach is recommended because this allows adequate assessment of metastases and good access to both kidneys and the inferior vena cava.

Addendum

Since this article was submitted, Case 5 has developed generalised metastases 18 months after the renal biopsies.

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Surgical Management of Idiopathic Retroperitoneal Fibrosis

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Summary—The management of 10 patients with idiopathic retroperitoneal fibrosis causing obstructive uropathy is presented. In all cases the obstruction was relieved by ureterolysis and corticosteroid therapy was not used during the initial treatment.

In 9 patients the operation was well tolerated but one, who developed a pyonephrosis after pre-operative ureteric drainage, died of septicaemia 15 days post-operatively. In 2 patients further explorations and ureterolysis were necessary for recurrent fibrosis which may have been related to urinary leakage. A policy for the management of these cases is presented which recommends the use of silastic tubing splints after ureteric mobilisation and the use of an omental wrap.

The clinical features of benign idiopathic retroperitoneal fibrosis have been well described (Ormond, 1948, Kerr *et al.*, 1968, Ross and Goldsmith, 1971; Mitchinson, 1972). The patients are usually male and middle-aged. They present typically with symptoms of loin or back pain, lethargy, loss of weight and disturbed gastrointestinal function. It is, however, the compression of the ureters and the resulting renal impairment which usually determine the outcome of the disease. There have been several reports of the treatment of the ureteric obstruction with corticosteroids both as an adjuvant to ureterolysis and as the sole therapy (Ross and Tinckler, 1958; Mitchinson *et al.*, 1971; Ochsner *et al.*, 1975; Clyne and Ambercrombie, 1977). Treatment with corticosteroids has been suggested to reduce the inflammatory oedema which obstructs urine flow (Mitchinson *et al.*, 1971; Ross and Goldsmith, 1971), to prevent further fibrosis after ureterolysis (Ross and Tinckler, 1958) and to inhibit maturation of fibroblasts (Charlton, 1968). The potential dangers of corticosteroid therapy are well known and because of these and the uncertainty of the response of retroperitoneal fibrosis to corticosteroids this treatment was avoided in the present series.

The clinical features and surgical management of 10 patients with obstructive uropathy due to retroperitoneal fibrosis are presented. The management of the cases in this series was not predetermined by protocol and was largely decided by the clinical circumstances. The problems which followed ureterolysis alone are discussed.

Patients and Methods

The 10 patients presented between the ages of 34 and 75. Nine were male and 1 female. The clinical features are summarised in Table 1. The plasma creatinine was raised in all patients on admission and in 8 it was more than 0.5 mmol/l (Table 1, Fig.).

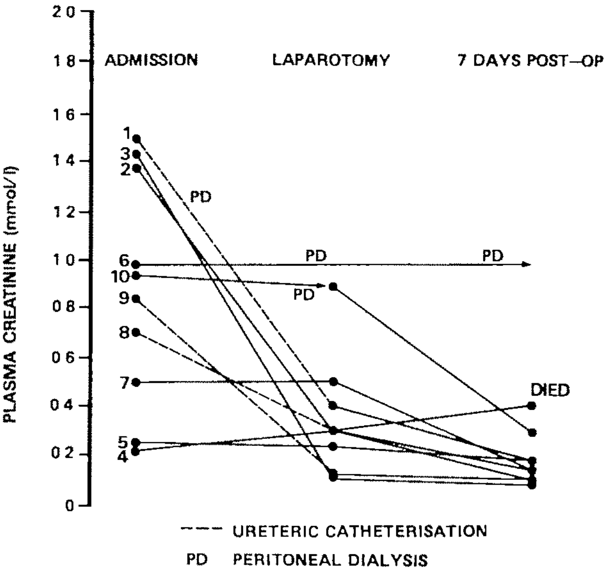

Fig. Plasma creatinine levels (mmol/l) on day of admission, at laparotomy and 7 days post-operatively

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Table 1 Summary of Clinical Details

No.	*Age in years*	*Sex*	*Presenting symptoms*				*Blood pressure mmHg*	*Plasma creatinine at presentation mmol/l*	*Intravenous urogram appearance of ureter*
			Pain	*Weight loss*	*Lethargy*	*Gastro-intestinal symptoms*			
1	34	M	Back	Yes	No	Diarrhoea and vomiting	170/80	1.5	Ureters not visualised
2	64	M	Epigastric	Yes	Yes	Bad taste	170/100	1.40	Ureters not visualised
3	64	M	Loin*	Yes	Yes	Vomiting	165/95	1.44	Moderate dilation of both ureters to the level of L4
4	67	M	Back and loin	Gained†	Yes	Nil	170/90	0.22	Ureters not visualised
5	65	F	Back	No	Yes	Diarrhoea and vomiting	120/80	0.21	Right ureter not visualised. Left ureter grossly dilated to L4
6	66	M	Nil	No	Yes	Nausea	160/90‡	0.97	Left ureter not visualised. Right ureter moderately dilated to L4
7	53	M	Epigastric	No	No	Nil	140/90	0.53	Left ureter not visualised. Right ureter moderately dilated to L3
8	75	M	Epigastric	Yes	No	Vomiting	160/100	0.7	Small left kidney Moderate dilation of upper right ureter
9	55	M	Loin and back	Yes	No	Nil	150/90	0.81§	Moderate dilatation of both ureters to L4
10	54	M	Loin, back and abdomen	No	No	Constipation	210/125‡	0.96	Ureters not visualised

* Had emergency appendicectomy 2 weeks prior to admission.
† Had extensive lower limb and sacral oedema.
‡ Previously treated for hypertension.
§ Anuric on admission.

High dose intravenous urography with tomograms demonstrated obstructive uropathy in all 10 patients either by negative pyelogram shadows during the nephrographic phase or distended calices in the delayed films. In 5 patients the ureters were demonstrated and retroperitoneal fibrosis was thought likely as the cause of obobstruction. In the remainder, retrograde pyelograms were necessary to demonstrate the level of obstruction.

Computerised tomography (CT) was performed pre-operatively in 3 patients (Cases 3, 4 and 5). In Case 4 no cause for ureteric obstruction was detected but appearances suggesting a right pyonephrosis were reported. In Cases 3 and 5 calcification was noted in the wall of the abdominal aorta which was encased in a mass of soft tissue. In Case 3 this soft tissue mass extended laterally to the ureters and retroperitoneal fibrosis was suggested. In Case 5 the mass was small and ureteric involvement was not detected.

Pre-operative Management

Three patients with mild renal impairment (Cases 4, 5 and 7) required no specific treatment before laparotomy. In Case 2, after treatment of hypertension and dietary protein restriction renal function improved spontaneously. In Case 3 there was a sustained diuresis and return to normal renal function after 1 g of frusemide given intravenously.

Ureteric catheters were passed endoscopically in 3 patients to relieve obstruction (Cases 1, 8 and 9).

Peritoneal dialysis was required in 3 (Table 2).

Details of Operation

The patients were explored transperitoneally through either a midline or paramedian incision with the exception of Case 8, in whom a right oblique muscle cutting incision was used. In this 75-year-old man the right ureter only was explored as his left kidney was small and scarred. In all cases after the identification of the areas of fibrosis representative biopsies were examined histologically by frozen sections. The appearances were of benign retroperitoneal fibrosis which was later confirmed by paraffin sections. The

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Table 2 Summary of Surgical Treatment and Results

No.	*Pre-operative management*	*Operation performed*	*Follow-up*	*Result plasma creatinine mmol/l*
1	Ureteric catheterisation and peritoneal dialysis	Ureterolysis, omental wrap and insertion of T-tubes × 2	7 years	0.09
2	Antihypertensives and diet	Ureterolysis and omental wrap	2 years	0.18
3	I.V. frusemide	Ureterolysis, omental wrap and insertion of silastic tubing × 2	18 months	0.09
4	—	Ureterolysis, omental wrap and insertion of silastic tubing × 2	15 days	0.61 Died of septicaemia
5	—	Ureterolysis, omental wrap and insertion of silastic tubing × 2	3 months	0.19
6	Peritoneal dialysis	Ureterolysis, omental wrap and insertion of T-tube	3 years	0.4
7	—	Ureterolysis and insertion of silastic tubing × 1	2 years	0.12
8*	Ureteric catheterisation	Ureterolysis and insertion of T-tube	1 year	0.15 Died of myocardial infarction
9	Ureteric catheterisation	1. Ureterolysis alone 2. Insertion of T-tube 3. Insertion of silastic tubing × 2	3 years	0.12
10	Peritoneal dialysis	1. Ureterolysis alone 2. Left hemicolectomy 3. Ureterolysis and insertion of T-tube in right ureter and silastic tubing in left ureter 4. Right nephrectomy	2½ years	0.2

* Patient with unilateral ureterolysis

ureters were then freed from the periureteric fibrosis, but where the ureteric wall was also involved dissection to the ureteric mucosa was necessary. After mobilisation the ureters were placed as far laterally as possible without tension. In 2 patients this was the sole treatment. In 5, omentum was wrapped around the ureter.

Latex T-tube splints were used in 5 patients. Silastic tubing (Dow Corning Corporation, either 0.192 or 0.125 inch external diameter) was used as a splint after freeing 10 ureters (Table 2). The silastic tubing was passed through a ureterotomy in healthy ureter so that it passed from the renal pelvis to the bladder. This was removed endoscopically with Lowsley's biopsy forceps at varying intervals of up to 11 months later.

Post-Operative Management

Only Case 6 required peritoneal dialysis post-operatively. In the remainder, with the exception of Case 4, the plasma creatinine fell as a result of ureterolysis to between 0.08 and 0.28 mmol/l by the seventh post-operative day (Fig.). The renal function of Case 4 deteriorated post-operatively and the creatinine rose to 0.4 mmol/l one week after the laparotomy.

Results

Case 4 died from septicaemia 15 days post-operatively. The infection originated from a pyonephrosis which followed a retrograde pyelogram performed before referral to this hospital.

Case 8 died from myocardial infarction one year after the operation, when renal function was satisfactory.

The remaining 8 patients are all well with follow-up of up to 7 years. The plasma creatinine is less than 0.2 mmol/l in 7 patients. In Case 6 the level is 0.4 mmol/l but he was known to have an elevated plasma creatinine level one year before retroperitoneal fibrosis was diagnosed.

Case 2 had a recurrence of his original symptoms 8 months following ureterolysis. His plasma creatinine level was unaltered at 0.18 mmol/l but because the ESR was elevated to 62 mm/1st h, he was commenced on prednisolone 5 mg twice a day. There was no response and as the CT scan failed to demonstrate any evidence of retroperitoneal fibrosis, prednisolone was discontinued. His only symptom when last reviewed was dyspepsia after alcohol.

Two patients required further exploration for recurrent fibrosis. Case 9 was re-explored 2 days after ureterolysis for increasing abdominal pain and oliguria. Extravasation from the right ureter was found and a T-tube was inserted temporarily. He was readmitted 8 months later with anuria, when a further laparotomy demonstrated dehiscence of the mid-part of both ureters with extravasation of urine. Silastic tubes were placed in both ureters and his renal function improved. At present his plasma creatinine is 0.12 mmol/l but a recent renogram demonstrated non-function of one kidney.

In Case 10, during the initial laparotomy and ureterolysis for benign retroperitoneal fibrosis a nodule was found at the junction of the descending and sigmoid colon. In view of the patient's poor general state, a resection of the lesion was not performed. Post-operatively a barium enema demonstrated a tumour and he underwent a left hemicolectomy for colonic adenocarcinoma. Eight months later there was marked deterioration of his renal function. Further exploration demonstrated recurrent benign periureteric fibrosis around both ureters and in particular on the left side at the site of the large bowel resection. A further ureterolysis was performed and a T-tube was placed in the right ureter and a silastic tube in the left ureter. He developed recurrent infections in the right kidney, leading to pyonephrosis for which he had a nephrectomy 15 months later. Two-and-a-half years following the original operation his plasma creatinine remains stable at 0.2 mmol/l, and there is no evidence of recurrence of the colonic tumour.

Discussion

The diagnosis of obstructive uropathy was made by intravenous urography in all 10 cases in this series. It is essential in patients with severe renal failure that a high dose of intravenous contrast be given (2 ml/kg BW/Urografin 325) and tomograms and delayed films taken for up to 24 h (Fry and Cattell, 1971). The diagnosis of obstruction may otherwise be missed, as was the case with examinations performed before referral in 2 of our patients. In 2 further patients retrograde pyelograms performed elsewhere were also reported as unobstructed. A major problem in the radiological diagnosis of retroperitoneal fibrosis is that the degree of pelvicaliceal and ureteric dilatation is often less than would be expected for the degree of renal failure (Lalli, 1977). In addition, ureteric catheters are often deceptively easy to pass, which may mislead the clinician. This has led Utz (1971) to propose that suppression of normal peristalsis in part accounts for the renal impairment in these patients. We feel that in these cases the diagnosis of obstructive uropathy should be made by intravenous urography (IVU). In view of the dangers of introducing infection with retrograde examination, it is now our policy to define the level of obstruction with retrograde ureterograms at the time of laparotomy.

In only 1 of the 3 cases in which CT scanning was used pre-operatively was the diagnosis confidently made and fibrosis may still be detected after successful ureterolysis, since the bulk of the tissue is not removed.

The initial management of patients with retroperitoneal fibrosis is concerned with the renal impairment. Ureteric catheters can usually be passed through the affected part of the ureters and this was done in 3 patients at the start of the series. However, if the catheters are draining from the renal pelvis to the outside there is always a risk of introducing infection, particularly if the renal pelvis is grossly distended and the urine flow rate low. This is emphasised in case 4, where the retrograde examination performed before referral produced a pyonephrosis which led to the patient's death from septicaemia. In view of the risk of infection it is our present policy to treat those cases with severe renal failure by dietary management and peritoneal dialysis prior to early laparotomy.

A transperitoneal approach for laparotomy and ureterolysis has 2 main advantages. Firstly, it permits a full laparotomy and assessment of the extent of fibrosis. Secondly, as both ureters are usually involved (Mitchinson, 1972), this approach enables both ureters to be explored. While releasing the ureter from the fibrosis it is not unusual to expose the ureteric mucosa in several places. Saxton *et al.* (1969) suggested that a nephrostomy may be performed in such cases. We believe, however, that silastic tubing placed along the entire length of the ureter is preferable and has 2 advantages. Firstly, the tube can be left *in situ* for many months with a reduced risk of infection and the problems inherent with nephrostomy. Secondly, if the renal impairment is partly due to the decreased peristalsis of the ureter (Utz, 1971; Lalli, 1977), the silastic tubing allows free drainage of urine from the kidney to the bladder. In the 2 cases in this series which required further exploration, no form of ureteric splintage or omental wrap had been used. It may be that urine leakage in these cases contributed to further fibrosis and it is now our practice to place silastic splints after ureterolysis and to perform omental wrap.

The use of silicone rubber tubing in patients with ureteric obstruction was suggested by Zimskind *et al.* (1967). Various silicone rubber catheters have been subsequently described which can be passed endoscopically (Gibbons *et al.*, 1974). However, as biopsies of the retroperitoneal fibrotic tissues are mandatory, we have in this series performed a laparotomy and passed the tubes through a ureterotomy.

The follow-up of these patients after ureterolysis has been by repeated clinical assessment, biochemical monitoring and radioisotope renography. In general we found, like Ross and Goldsmith (1971), that plasma creatinine is the most useful index of renal function, since minor changes of the IVU or the renogram are difficult to evaluate. The ESR was found to be an unreliable guide to the state of retroperitoneal fibrosis. At the time of admission, when the patients were in renal failure, it was grossly elevated and after relief of the obstruction it fell to near normal. In agreement with Kinder (1979), we have also found that the ESR may fall, although the bulk of the plaque is not removed. Also, although there were fluctuations of the ESR in the follow-up period, there was no correlation with symptoms in our patients.

In this series 7 patients had good control of the disease with surgery alone with a follow-up of 3 months to 7 years. In the other 3 we do not feel that steroid therapy would have helped. In the patient who died of septicaemia, corticosteroid therapy would almost certainly have exacerbated the problem. The 2 patients who had repeated laparotomy were both initially treated by ureterolysis alone and it is our present practice to splint ureters and perform omental wraps in all patients. Although this is a relatively small series, it remains our policy not to prescribe corticosteroids to patients with idiopathic retroperitoneal fibrosis but to rely on the surgical relief of obstruction.

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Percutaneous Nephrolithotomy

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Summary—Small mobile stones in the major renal collecting system can be extracted through a percutaneous tract. Initially the radiologist performs a conventional percutaneous needle nephrostomy and inserts a pigtail catheter into the renal pelvis. Over the next week the tract formed is serially dilated to a size large enough to pass a cystoscope into the kidney. The calculi are trapped by a stone basket and removed. The many advantages of this relatively atraumatic procedure are discussed.

The need to make a large and traumatic loin incision to extract a relatively small calculus from the renal collecting system has always been a major disadvantage of renal surgery for stones.

In the last few years, the increasing facility for performing a percutaneous nephrostomy by radiologists has added a new dimension to the management of the small mobile renal calculus within the major collecting system. The ability to pass a fine nephrostomy tube into the kidney by direct percutaneous puncture, dilate the tract and then insert some sort of optical or non-optical device to remove the stone has now become an attractive proposition. Such a concept has been developed by Alken and Günther from Mainz in West Germany (Günther *et al.*, 1978).

We felt that this method should be explored further and we have, to date, removed stones from the interior of the kidney by percutaneous puncture in 4 cases.

Materials and Methods

The patients selected for treatment were those in whom the intrarenal collecting system was reasonably dilated and within which there was a small calculus not more than 2 cm in transverse diameter (Fig.). In most cases the mobile calculus had been causing intermittent pelviureteric junction obstruction and considerable pain and discomfort to the patient, often coupled with haematuria and urinary tract infection.

Initially, a percutaneous needle nephrostomy was inserted by the radiologist in the conventional way. A teflon-sheathed needle was introduced under local anaesthesia into the major renal collecting system. This was performed with the patient in a prone oblique position in order to gain access to the collecting system trans-parenchymally. Once the collecting system was entered satisfactorily, the needle was removed and a fine guide wire was passed through the teflon sheath into the renal pelvis. Small dilators were then introduced over the guide wire, to enable the insertion of an 8 FG pigtail catheter. If this was found to be lying in a good position it was then secured at the skin surface and the patient allowed to remain either in hospital or to return home.

Two days later the patient was seen again and the guide wire again passed through the catheter, which was then removed. Serial dilators were then passed over the guide wire to stretch the size of the nephrostomy tract to about 14 or 16 FG. In the absence of significant bleeding a similar sized nephrostomy tube was passed into the kidney and allowed to remain *in situ*.

Two days later a similar process was repeated, this time taking the size of the nephrostomy tract up to about 22 to 26 FG, depending upon the size of the stone. On the day after this dilatation the patient was taken to the X-ray theatre, the nephrostomy tube was removed and the patient was sedated with Valium and Pethidine. A standard Storz 21 French cystoscope with a 30° telescope was passed along the tract of the nephrostomy tube into the interior of the kidney. Irrigation was by means of normal saline.

In each case it was found that the stone could usually be easily identified lying within the renal pelvis. A Pffister-Schwartz stone-remover was introduced. The stone basket was manoeuvred

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Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

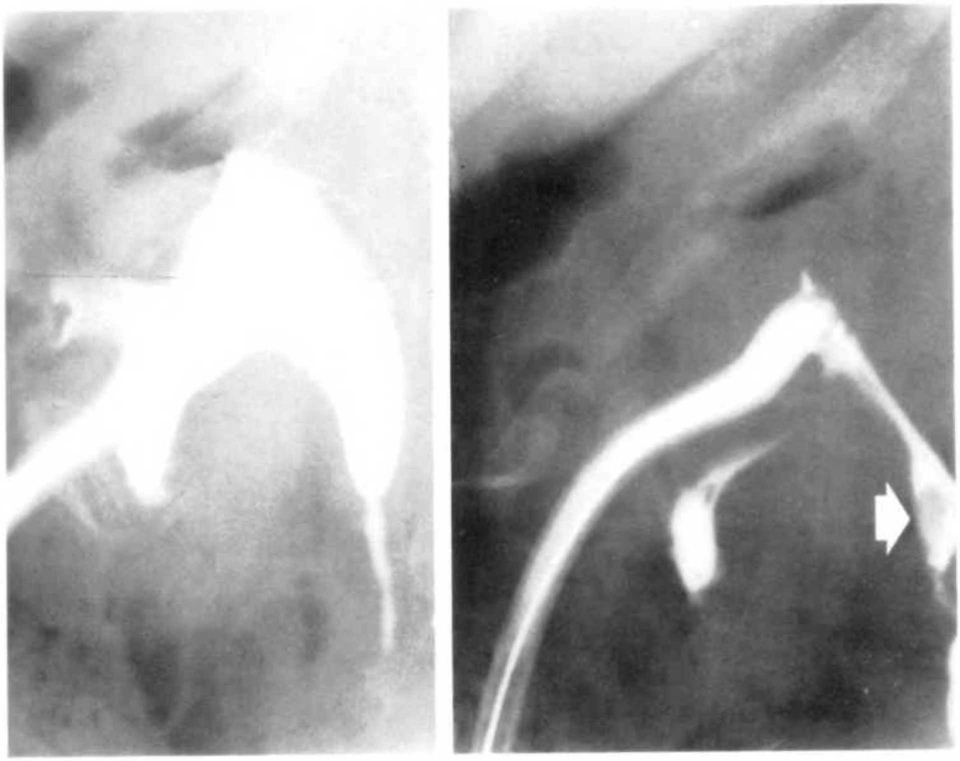

Fig. A calculus (arrow) is seen in the renal pelvis, a 24 FG nephrostomy tube lying above it.

to secure the stone and then the whole cystoscope, together with the stone and stone-remover, was withdrawn through the nephrostomy tract.

The procedure was usually carried out with very little discomfort to the patient. There was no attempt to suture the nephrostomy tract, which in all cases closed spontaneously within the next 24 h. The patient was able to leave hospital on the day after the procedure.

Results

Of the 5 cases in which this technique has been used, 4 resulted in successful extraction of the stone. In the fifth case there was some difficulty in placing the nephrostomy tube, which took an oblique course through the overhanging lip of the renal parenchyma into the renal collecting system and presumably disrupted the posterior wall of the renal pelvis; when the cystoscope was introduced down the tract it was impossible to identify the renal pelvis. The procedure was therefore abandoned; the patient was anaesthetised and the stone extracted by conventional pyelolithotomy.

In the remaining 4 cases the stone was extracted easily without serious complication. During the initial needle nephrostomy in one patient there was some arterial bleeding, presumably from a capsular vessel which arrested when the pigtail catheter was inserted. There was no persistent fistula in any of the cases. All 4 patients were well satisfied with the procedure and the fact that major operation was no longer indicated.

Discussion

It is advantageous and far less traumatic to remove small stones from the intrarenal collecting system by the technique described. Not only is there no long-term hospitalisation, but the morbidity is small when compared with that inflicted by a conventional loin incision.

We have restricted the technique to stones that are free within the renal pelvis, but with the development of a flexible nephroscope which is being produced by an English firm it should be possible to extend the indications to stones in peripheral calices. This nephroscope will have the facility of turning the tip of the instrument through 180° and be able to negotiate the caliceal neck. In this way it should be possible to undertake the removal of more peripheral calculi in the collecting system.

It is suggested that this form of endoscopic manipulation of intrarenal calculi will rapidly become an established procedure for the removal of these calculi and that the more traumatic approach will gradually become obsolete.

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The Single Ectopic Ureter and the Dysplastic Kidney

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Summary—Eight children, 3 girls and 5 boys, with single ectopic ureters arising from non-concentrating kidneys are described. Two children, both girls, complained of persistent wetting with a pattern suggestive of ectopic ureter: 2 of the boys presented in the neonatal period with massive abdominal distension: the remaining children developed a urinary infection or chronic urinary retention.

Diagnosis depends on an appreciation of the possibility that a non-concentrating kidney on intravenous urography may be giving rise to an ectopic ureter and, in the boys, on a correct interpretation of cystourethrographic findings. Careful endoscopic examination of the urethra and in the girls of the vagina also will lead to the identification of the ectopic ureteric orifice in most cases. When the ectopic ureter joins the male genital tract there may be an extravesical ureterocele which can be recognised cystoscopically.

The condition is treated by nephroureterectomy.

In young girls, persistent wetting caused by an ectopic ureter from a duplex kidney is a familiar syndrome to paediatric urologists, but wetting caused by a single ectopic ureter, particularly when the ureter arises from a dysplastic non-concentrating kidney, may not be recognised, perhaps because the condition is alleged to be rare (Gibbons and Duckett, 1978). Furthermore, though commoner and better described (Cendron and Bonhomme, 1968; Johnston and Davenport, 1969; Williams and Royle, 1969; Schulman, 1976), the characteristic features of the similar condition in the male child may not be appreciated. The purpose of this paper is to describe 8 children, 5 boys and 3 girls, each of whom was found to have a single ectopic ureter arising from a dysplastic kidney.

Patients

The cases can be divided into groups according to their anatomical patterns as advocated by Williams and Royle (1969), except that a special group for the females is required in this series. The case histories are summarised in the Table.

Group I (Female) Vaginal Ectopic Ureter There were 2 children, aged 6 years 10 months (Case 1) and 7 years 7 months (Case 2) in this group. They had identical histories except that in one the left kidney was affected and in the other the right. The presenting complaint was of persistent wetting of the ectopic ureter pattern, *i.e.*, con-

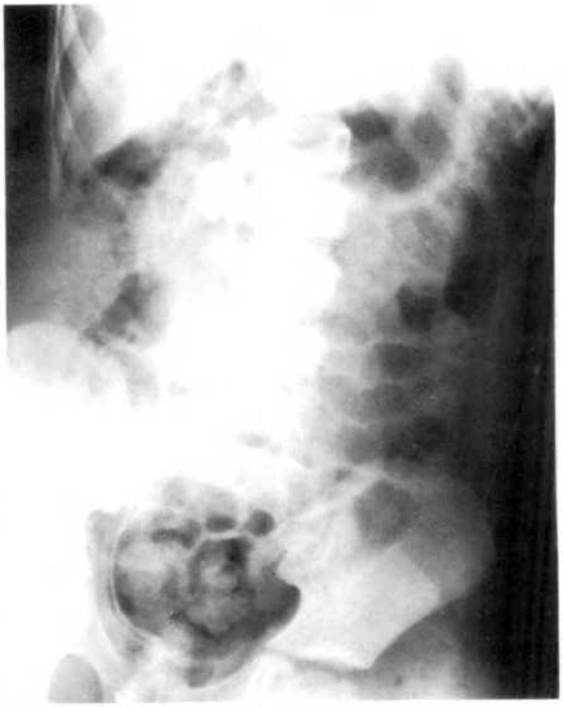

Fig. 1, Case 1 Retrograde pyelogram through right ectopic vaginal ureteric orifice.

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Table Single Ectopic Ureter with Dysplastic Kidney. Summary of Cases

Group	*Case No.*	*Sex*	*Age*	*Presenting symptom*	*Radiology*		*Pathology*
					IVU	*Cystourethrogram*	
I (F) Vaginal ectopic ureter	1	F	6 years 10 months	Wetting	Absent RK	Normal	Dysplasia
	2	F	7 years 7 months	Wetting	Absent LK	Normal	Dysplasia
I (M) Urethral ectopic ureter	3	M	1 day	Abdominal mass (R)	Absent RK	Funnel-shaped posterior urethra	Dysplasia
	4	M	1 week	Abdominal mass (L)	Absent LK	Funnel-shaped posterior urethra	Dysplasia
II Urethral ectopic ureter with ureterocele	5	F	1 year 11 months	Acute UTI	Absent RK Ureterocele in bladder	Right ureterogram	Hydronephrotic atrophy
III Urethral ectopic ureter with extravesical ureterocele	6	M	6 years 6 months	Recurrent UTI	Absent LK Dilated RK	Funnel-shaped posterior urethra	Dysplasia
	7	M	8 years 9 months	Urinary retention and dribbling	Absent RK Dilated LK and ureter	Funnel-shaped posterior urethra	Dysplasia
IV Ectopic ureter with genital tract connection	8	M	3 years 4 months	Urinary retention and dribbling	Absent RK	Could not void	Dysplasia

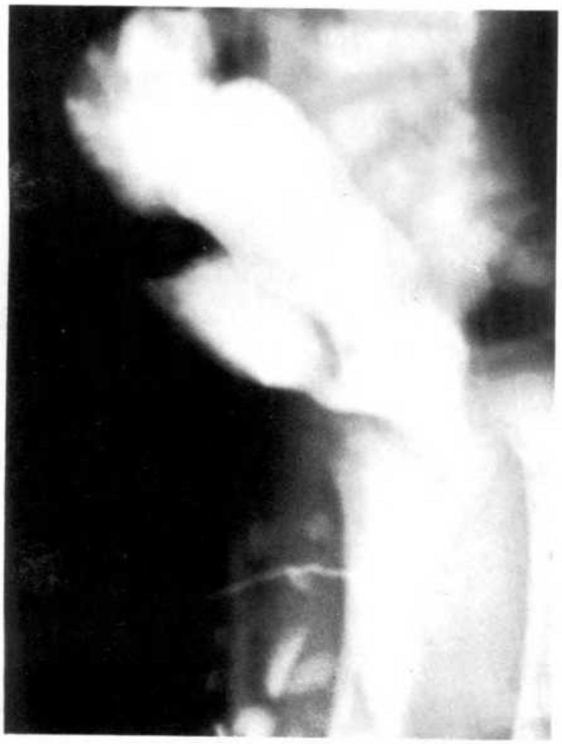

Fig. 2, Case 4 Micturating urethrogram showing reflux into grossly dilated left ureter which is terminating in funnel-shaped posterior urethra.

tinuous diurnal dampness despite micturating at normal intervals and passing apparently normal volumes of urine. Both sets of parents had been told that their children had simple enuresis which would improve with time.

On examination in the clinic the only abnormal physical sign was noted in the vulval area, where urine could be seen slowly emerging, but it was

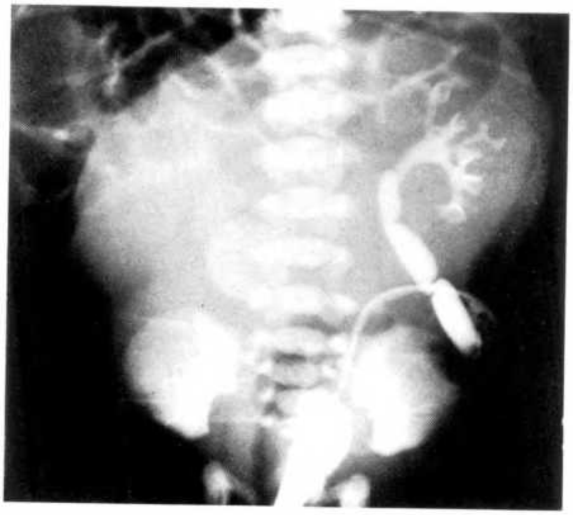

Fig. 3, Case 3 Retrograde pyelogram through orthotopic left ureteric orifice shows gross lateral displacement of lower ureter.

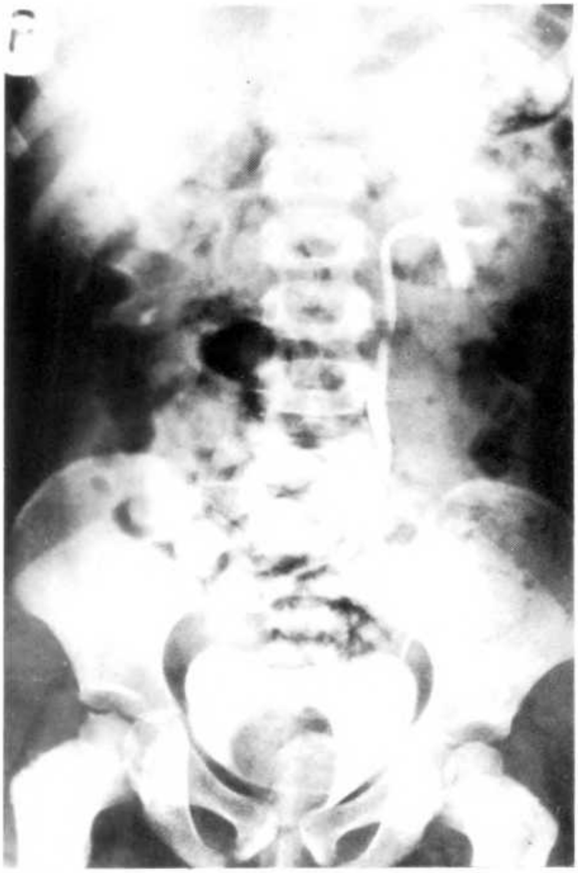

Fig. 4, Case 5 Intravenous urogram showing normal left kidney, no concentration in the right kidney and a large right ectopic ureterocele.

impossible to ascertain the exact point from which it was coming. Intravenous urography (IVU) failed to demonstrate one kidney; the contralateral upper urinary tract and bladder were normal. Cystography was also normal. Cystoscopy showed a normal bladder except that one ureteric orifice was absent; the urethra was also normal. Having failed to discover a ureteric orifice in the vulva, the vagina was then examined with the cystoscope. Eventually a ureteric orifice was seen in the lateral wall on the appropriate side and it was possible to insert a ureteric catheter and perform retrograde pyelography. This demonstrated a small kidney in the lumbar region (Fig. 1). The children were treated by nephrectomy with excision of the lumbar ureters. Postoperatively, the symptoms completely disappeared.

Group I (Male) Urethral Ectopic Ureter There were 2 children in this group, aged 1 day (Case 3) and 1 week (Case 4) at presentation and, as in the previous group, both had identical histories except that different sides were affected. Marked abdominal distension had been noted soon after birth and on examination there was a tense cystic swelling occupying the whole flank which extended across the midline. Intravenous urography failed to demonstrate the kidney on the side of the swelling. Cystourethrography showed a funnel-shaped dilatation of the posterior urethra and in one infant there was reflux into the grossly dilated ectopic ureter (Fig. 2). Endoscopy revealed the ectopic ureteric orifice in the posterior urethra. The degree of the ectopic ureteric dilatation was demonstrated indirectly in one of the infants by retrograde pyelography through the orthotopic orifice; there was gross lateral displacement of the lower ureter (Fig. 3). The enormously dilated kidneys and ureters were excised at laparotomy, the ureters being dissected out of the wall of the bladder and divided as close as possible to the posterior urethra. Both children are now symptom-free.

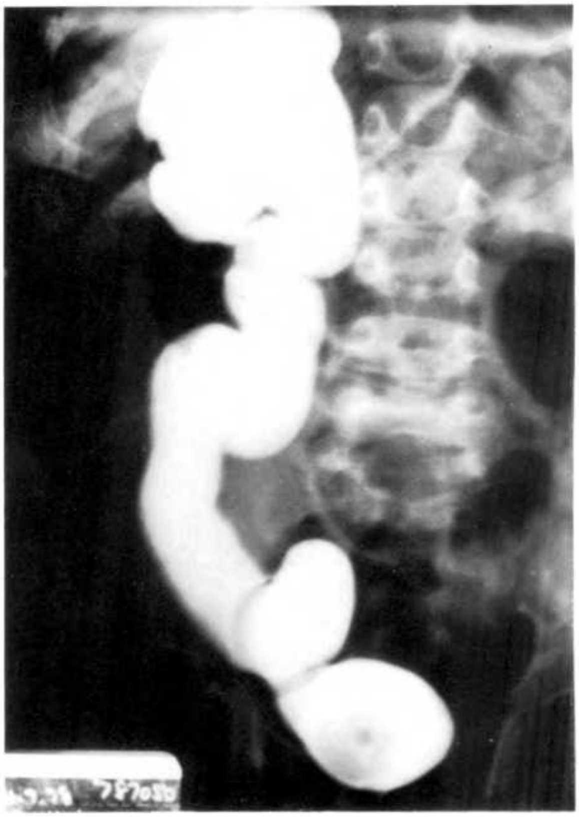

Fig. 5, Case 5 Attempted cystogram. Catheter has passed through urethral ectopic ureteric orifice and contrast reveals a single right kidney.

Group II—Urethral Ectopic Ureter with Ureterocele There was 1 child (Case 5) in this group, a girl aged 1 year 11 months, who presented with an acute urinary tract infection. Intravenous urography failed to demonstrate the right kidney but showed a ureterocele on the right side of the bladder (Fig. 4). Cystography was attempted but when the contrast medium was run in, it was clear that the catheter had entered the ectopic ureter (Fig. 5). Nephroureterectomy was performed.

Group III—Urethral Ectopic Ureter with Extravesical Ureterocele There were 2 children, both boys, in this group, aged 6 years 6 months (Case 6) and 8 years 9 months (Case 7).

The younger boy presented with an acute urinary infection and right loin pain. The intravenous urogram showed a dilated right kidney containing a stone but the left kidney was not seen. A cystourethrogram (Fig. 6) demonstrated a funnel-shaped posterior urethra. Endoscopy confirmed the presence of an ectopic ureteric orifice in the left wall of the posterior urethra through which a ureteric catheter was passed to obtain a retrograde ureterogram. At operation the left kidney was found in the loin and removed together with the ectopic ureterocele. Subsequently a right pyeloplasty with removal of the stone was carried out.

The older boy complained of difficulty with micturition and persistent urinary dribbling. On examination his bladder was palpably distended. Intravenous urography failed to demonstrate the right kidney and showed marked dilatation of the whole left upper tract (Fig. 7). Cystography revealed an appearance suggestive of neuropathic bladder (Fig. 8). The micturating cystogram did not properly demonstrate the urethra because the boy was able to pass urine with only a poor stream. The results of a cystometrogram and bethanechol stimulation test were characteristic of occult neuropathic bladder. Nothing remarkable was noted on endoscopy except that the right ureteric orifice was missing. The boy was treated for 8 months with gradually increasing doses of oral bethanechol chloride without improvement in his symptoms. A further IVU showed that the left upper tract dilatation had increased and a cystourethrogram on this occasion revealed a funnel-shaped posterior urethra. On endoscopy, with particular attention to the posterior urethra, an ectopic ureteric orifice was seen through which a ureteric catheter was passed, permitting retrograde pyelography (Fig. 9). At operation a small but normally located dysplastic kidney was removed together with the ureter and ureterocele. For a month post-operatively the boy's bladder function improved but retention and dribbling gradually returned.

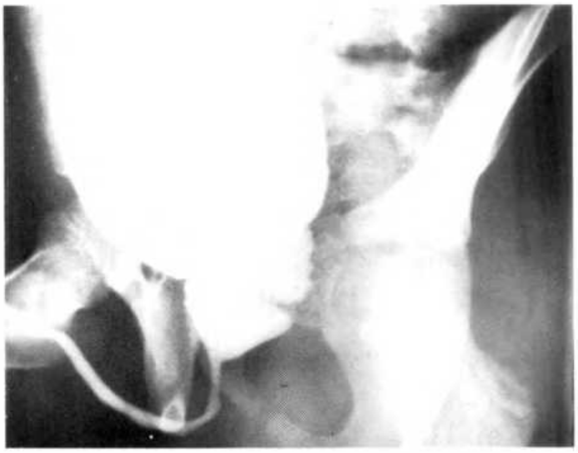
Fig. 6, Case 6 Micturating urethrogram showing funnel-shaped posterior urethra and extravesical ureterocele.

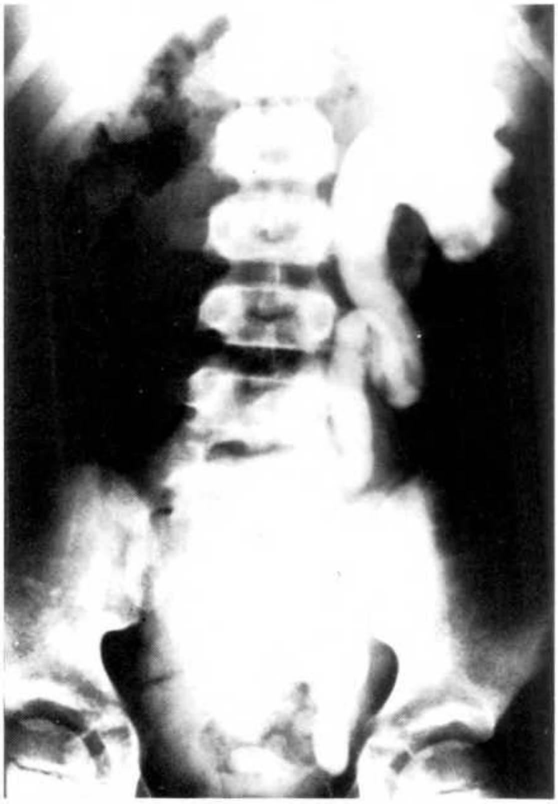
Fig. 7, Case 7 Intravenous urogram showing dilated left upper urinary tract but no concentration in right kidney.

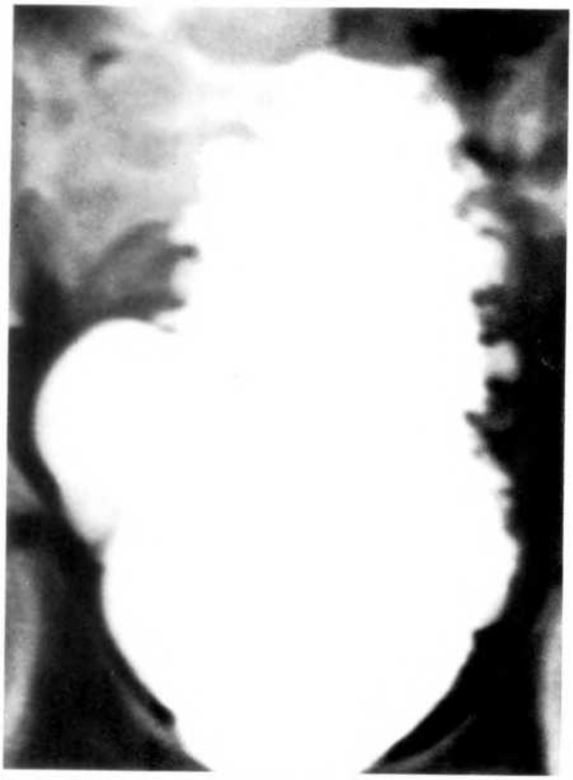

Fig. 8, Case 7 Cystogram reveals appearances of neuropathic bladder.

Group IV—Ectopic Ureter Involving Genital Tract

There was 1 child (Case 8) in this group, a boy of 3 years 4 months who presented with a 10-week history of difficulty with micturition and dribbling; the bladder was palpable on physical examination. Intravenous urography failed to demonstrate the right kidney but the left kidney was normal. The posterior urethra was normal on endoscopy but a large ureterocele could be seen bulging into the right side of the bladder, the trigone and the bladder neck, so that detailed examination was impossible. The lower end of the right ureter was explored and found to be grossly dilated. When traced distally it entered a huge ureterocele which was dissected out of the pelvis and bladder wall with some difficulty: eventually it was found to be communicating with the right seminal vesicle. Proximally, the ureter joined the pelvis of a small dysplastic kidney in the loin, which was removed together with the ureter and ureterocele.

Discussion

The embryology of the single ectopic ureter and dysplastic kidney is fully described by Williams and Royle (1969) and Schulman (1976) and will not be further debated here. The condition may be mis-diagnosed because the significance of the non-concentrating kidney on intravenous urography is not recognised. Cases 1 and 2, the girls with vaginal ectopic ureters, were regarded as having simple enuresis and coincidentally an absent kidney, until a precise history of the pattern of their wetting led to a determined search for an ectopic ureter and careful endoscopic examination of their vaginae. In the boys, the urethrographic finding of a funnel-shaped dilatation of the posterior urethra may be missed or even misinterpreted as obstructive dilatation caused by posterior urethral valves. When the ectopic ureterocele causes bladder outflow obstruction and urinary retention, a satisfactory micturating cystourethrogram may be impossible to obtain, as in Case 7. But here again, diagnosis rests on careful endoscopy and the discovery of an ectopic ureteric orifice in the urethra. If the

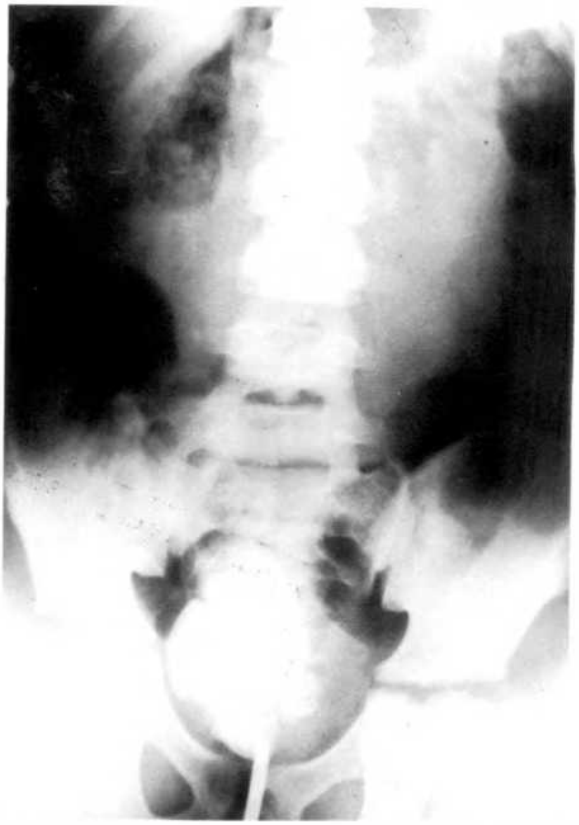

Fig. 9, Case 8 Retrograde pyelogram through right ectopic urethral orifice reveals dilated lower ureter and extravesical ureterocele.

ectopic ureter enters the genital tract there may be a ureterocele which deforms the lateral and inferior walls of the bladder, as in Case 8. When no ureterocele is present, the presenting symptoms may be of epididymitis, but these patients do not usually present until adult life (Schnitzer, 1965; Gordon and Kessler, 1972; Fuselier and Peters, 1976; Mellin *et al.*, 1976).

With one exception, the histological examination of the excised kidneys demonstrated gross dysplasia with sparse, abnormal glomeruli, fibrosis and cyst formation. The exception was Case 5, where the changes were due to simple obstructive atrophy. It is noteworthy that she had the least "ectopic" ureter in the whole series.

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The Value of Intravesical Prostaglandin E_2 and $F_{2\alpha}$ in Women with Abnormalities of Bladder Emptying

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Summary—A clinical study of intravesical prostaglandin E_2 (PGE_2) and $F_{2\alpha}$($PGF_{2\alpha}$) in the treatment of 13 female patients with difficulties in emptying their bladder is reported. Urodynamic investigations were performed before and after instillation of the drug. Although 3 patients had some reduction in residual urine volume, the remainder showed no obvious change and no patient experienced subjective improvement. In 6 patients, biopsies of the vesical mucosa were taken before and after instillation in order to measure the uptake of prostaglandin by the mucosa, but no conclusions could be drawn from these measurements.

Although prostaglandins are known to have contractile effects on the detrusor muscle, the results of this study suggest that intravesical PGE_2 and $PGF_{2\alpha}$ have no therapeutic value in the treatment of voiding dysfunction and residual urine.

Medical treatment of impaired voiding with chronic retention of urine often proves ineffective. When there is no mechanical bladder outlet obstruction and the detrusor muscle fails to contract, the administration of cholinergic agents such as carbachol is the usual treatment. Nevertheless, one is often confronted with the clinical ineffectiveness and the unacceptable systemic side effects of these drugs. In some cases, moderate success may be expected from the administration of alpha-blocking agents such as phenoxybenzamine, with the aim of decreasing urethral resistance. Therefore there is a clear need for drugs that will induce or augment detrusor contractility as well as decrease outflow resistance (Bissada, 1979). It seems that PGE_2 is able to stimulate the bladder while reducing the urethral tone.

Recently, Bultitude *et al.* (1976) and Andersson *et al.* (1978) reported success with the intravesical instillation of PGE_2 in female patients with difficulty in micturition and chronic or acute retention. Animal experiments have shown that PGE_2 and $PGF_2\alpha$ have contractile effects on isolated strips of detrusor muscle (Ambache and Zar, 1970; Bultitude *et al.*, 1976; Hills, 1976; Khanna *et al.*, 1978).

Human studies have demonstrated that $PGF_2\alpha$ has the most potent contractile effect upon bladder muscle, approaching that of acetylcholine (Abrams and Fenely, 1976). On the other hand, Khanna *et al.* (1978) stated that the stimulating effect of PGE_2 on bladder muscle of the rabbit was twice that of $PGF_2\alpha$.

The action of PGE_2 and $PGF_2\alpha$ on urethral smooth muscle is controversial; it seems that PGE_2 reduces urethral resistance (Persson, 1976; Andersson *et al.*, 1977, 1978), but this relaxing effect on the urethra was not noted by Khanna *et al.* (1978).

Prostaglandin $F_2\alpha$ has been shown to have contractile effects on the urethra (Andersson *et al.*, 1977; Khanna *et al.*, 1978).

In the present study, the action of intravesical PGE_2 and $PGF_2\alpha$ has been assessed in female patients with difficulties in emptying their bladder. The effects were assessed by urodynamic studies carried out before and after instillation. In some cases the absorption of prostaglandin through the vesical mucosa was studied by radioimmunoassay (RIA) of prostaglandins in biopsies taken before and after instillation.

Patients and Methods

Thirteen female patients with difficulties in emptying their bladder were investigated and treated with either PGE_2 or $PGF_2\alpha$. Their ages ranged from 18 to 75 years (mean 47 years).

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Table 1

Number of patients	*Case number*	*Aetiology of voiding dysfunction*
5	(1, 2, 7, 8, 13)	Unknown
4	(3, 9, 11, 12)	One or more previous anterior vaginal repairs
1	(4)	Prolonged bladder distension for nocturnal enuresis
1	(6)	Multiple sclerosis
1	(10)	Occult neuropathic bladder
1	(5)	Post-operative overdistended bladder

Eighteen bladder instillations were performed, 13 with PGE_2 and 5 with $PGF_2\alpha$.

Nearly all patients had received previous treatment with carbachol without success. About half of the patients had received phenoxybenzamine, which had also failed to relieve their symptoms. The causes of their problems are listed in Table 1.

Each woman underwent a full urodynamic examination, including a filling and micturating cystometrogram and a urethral pressure profile, just before the application of the drug. The bladder was filled at a constant rate of 50 ml/s. Special attention was paid to functional bladder capacity, detrusor pressure at maximum flow, abdominal straining during micturition, maximum flow rate and residual urine volume. Additional abdominal straining to urinate was found in all patients; 7 patients had a completely atonic bladder and 4 of these failed to micturate. All patients had residual urine volumes ranging from 50 to 1100 ml, with an average of 470 ml. The urodynamic measurements are presented in Table 2.

The urethral pressure profile was performed according to the method of Brown and Wickham (1969). It is important to mention that any evidence of mechanical bladder outlet obstruction could be excluded by means of urethral calibration, endoscopy, pressure/flow analysis and micturating cystourethrography.

In 6 patients biopsies of the vesical mucosa were taken during cystoscopic examination, in order to determine the concentration of PGE_2 and $PGF_2\alpha$ before application of the drug. The tissue samples were immediately frozen in liquid nitrogen and stored at −70°C until assay. Then the

Table 2

Pat no.	*Age (years)*	*PG; dose*	*Duration of instillation (min)*	*Before prostaglandins*				*After prostaglandins*			
				Bladder capacity (ml)	*Residual urine (ml)*	*Max flow rate (ml/s)*	*Max flow pressure (mmHg)*	*Bladder capacity (ml)*	*Residual urine (ml)*	*Max. flow rate (ml/s)*	*Max. flow pressure (mmHg)*
1	54	E_2; 0.5 mg	30	1100	1100	0	0	750	730	2	0
2	25	E_2; 0.5 mg	30	650	650	0	0	470	470	0	0
		E_2; 0.5 mg	30	720	720	0	0	650	650	0	0
3	70	E_2; 0.5 mg	30	260	100	10	11	480	30	17	16
		$F_2\alpha$; 2 mg	60	300	120	8	10	320	60	8	12
4	18	E_2; 0.5 mg	30	500	500	0	0	550	550	0	0
		E_2, 5 mg	30	600	600	0	0	580	580	0	0
		E_2; 10 mg	120	600	600	0	0	650	650	0	0
5	38	E_2; 1 mg	60	800	720	8	34	750	500	20	40
6	48	E_2; 2 mg	60	1000	900	5	0	1000	750	6	0
7	75	E_2; 5 mg	30	450	300	8	15	300	280	4	15
8	64	E_2; 5 mg	30	500	250	10	12	625	225	12	24
9	39	E_2; 5 mg	60	450	450	0	0	500	500	0	0
		E_2; 10 mg	90	500	500	0	0	600	350	15	8
10	23	$F_2\alpha$; 1 mg	30	700	200	36	22	760	80	30	40
11	35	$F_2\alpha$; 5 mg	60	520	260	13	32	530	530	0	0
12	58	$F_2\alpha$; 5 mg	60	630	450	10	0	550	410	16	6
13	64	$F_2\alpha$; 5 mg	60	400	50	8	0	350	20	13	0
Mean	47	—	—	593	470	6.4	7.5	579	409	7.9	8.9

frozen tissue was weighed, washed once in isotonic saline and homogenised in a small Potter-Elvehjem glass homogeniser. Prostaglandins were determined according to the method previously described by Thomas *et al.* (1978a, b).

After urodynamic investigation the bladder was emptied through a urethral catheter and a known amount of PGE_2 or $PGF_2\alpha$ was dissolved in 50 ml sterile distilled water and instilled into the bladder (Table 2). The drug was kept in the bladder for 30 min in 9 patients, 60 min in 7 patients, and 90 and 120 min in 2 patients. The cystometrogram and the urethral pressure profile were repeated at the end of this procedure. In the patients who underwent a bladder biopsy before treatment, a new biopsy was taken after instillation and this was also immediately frozen in the same way.

Results

In general, the urodynamic parameters did not change significantly after instillation (Table 2). Although the data obtained from the urodynamic study after instillation showed some improvement in the micturition pattern (nos. 1, 2 and 9), none of the patients benefited subjectively from the treatment. Three patients (nos. 2, 3 and 10) felt some urgency and suprapubic discomfort at the end of the instillation, but these complaints disappeared within 24 h. We observed no differences between the urethral pressure profiles recorded before and after treatment. The results of the biopsies are shown in Table 3.

Higher doses of the drug (>0.5 mg) and/or a longer instillation time did not affect the results.

Discussion

Bultitude *et al.* (1976) were the first to use PGE_2 intravesically and they noted a response in 14 of 21 females with voiding inefficiency. They instilled the bladder with only 0.5 mg PGE_2 during 30 min.

Although prostaglandins have a relatively short half-life (Piper *et al.*, 1970), the effects after a single application of PGE_2 lasted in many patients for several months, and even up to 2 years. Andersson *et al.* (1978) were not able to reproduce these favourable effects with a dose of 0.5 mg PGE_2. They used doses ranging from 4 to 10 mg (mostly 5 mg) and in this way a small increase in bladder pressure was shown immediately after treatment in the 9 females studied. However, none of these effects persisted at re-examination after 7 to 10 days.

To our knowledge, there have been no previous studies using intravesical $PGF_2\alpha$ in patients with dysuria and residual urine. The fact that, in our study, no beneficial effects were noted following administration of PGE_2, even with doses of 10 mg, prompted us to try $PGF_2\alpha$. Moreover, Abrams and Fenely (1976) demonstrated that the contractile effect of $PGF_2\alpha$ was greater than that of PGE_2 on human bladder muscle. Again, $PGF_2\alpha$ was ineffective in restoring bladder function in our patients.

Measurements of the biopsies of vesical mucosa taken before and after instillation did not allow conclusions to be drawn regarding the uptake following instillation: about half of the pairs tested showed either an increase or a decrease in prostaglandin levels in the tissue.

In additional control experiments (4 normal functioning bladders) the prostaglandin concentrations were determined in 2 simultaneous biopsies (left and right sides) from the same bladder, and the levels measured showed a 2-fold

Table 3

Pattern no.	*Age (years)*	*PG; dose*	*Duration of instillation (min)*	*Tissue concentrations of prostaglandins* in biopsies taken before and after instillation*			
				$PGF_{2\alpha}$		*PGE_2*	
				Before	*After*	*Before*	*After*
1	54	E_2, 0.5 mg	30	938	537	68	99
2	25	E_2; 0.5 mg	30	633	249	378	37
3	70	E_2; 0.5 mg	30	164	153	91	88
4	18	E_2; 0.5 mg	30	850	921	190	381
5	38	E_2; 1 mg	60	958	1161	366	190
10	23	$F_2\alpha$; 1 mg	30	99	51	256	381

*Means of duplicate measurements; values are expressed in pmol PG/g frozen tissue.

variation. This can be explained by the presence of aggregating blood platelets that are known to synthesise and release prostaglandins (Smith and Willis, 1970). Furthermore, surgical trauma is also associated with a marked increase in prostaglandin content (Änggård and Jonsson, 1972), thus probably leading to unreliable determinations of prostaglandin tissue levels in biopsies.

It is concluded that despite the known effects of PGE_2 and $PGF_2\alpha$ on bladder muscle tone and contractility, these drugs appear to be ineffective in the treatment of patients with difficulty in micturition.

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A Long-term Study of the Persistence of the Urodynamic Characteristics of the Unstable Bladder

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Summary—Sixty-four patients with normal bladder function, stress incontinence, idiopathic instability or instability associated with enuresis underwent pressure/flow videocystography. This was repeated from one month to 8 years later (average 19.4 months).

Filling cystometry remained qualitatively unchanged in 95% of cases overall, whilst the actual pressure recordings during cystometry in the 37 patients with instability remained identical or very similar in 73%.

The results demonstrated the accuracy of cystometry and the consistency of bladder dynamics over the longest period so far reported in these apparently non-progressive disorders.

Repeated urodynamic evaluation of patients with normal bladder function or a non-progressive unresolved bladder dysfunction is not often indicated. However, in a series of over 11,000 examinations performed in our urodynamic clinic at the Middlesex Hospital over the last 12 years, we have had the opportunity to assess both the reproducibility of bladder function measurements and, in certain conditions, the long-term behaviour of the bladder. These observations are fundamental if cystometry and voiding pressure/flow recordings are to be used as objective criteria upon which the management of clinical problems and the results of therapy are to be assessed.

Patients and Methods

The technique of synchronous pressure/flow/cystourethrography developed at the Middlesex Hospital in 1969 (Bates *et al.*, 1970; Bates and Corney, 1971) has changed little, apart from the substitution of cine-film by video-recording. This synchronous study is a convenient routine for a referral unit to use for the study of bladder function and dysfunction during both filling and voiding phases.

This communication was based upon an aliquot of 64 patients who underwent a number of re-examinations—145 in all—after varying intervals; the average interval time was 19.4 months with a range between 1 month and 8 years from the first to last examination.

In order to reduce the many variable factors as much as possible no patient included in this study had ever had:

1. Urinary tract surgery, gynaecological or other pelvic surgery, obvious pelvic inflammatory disease.
2. Conditions likely to affect the bladder function, *e.g.* neuropathy, diabetes, trauma.
3. Bladder outflow obstruction.

The patients were divided into 4 groups on the basis of the findings of their first videocystogram and their clinical history (Table 1). It so happened that the average time interval between the first and last examination in each group differed little.

Group III patients were described as having "idiopathic instability" since their instability was unrelated to any obvious aetiological feature such as outflow obstruction or neuropathy.

Patients in Group IV were classified thus if they had either unstable cystometry and a history of life-long enuresis or a history of childhood enuresis beyond the age of 7 years. The type of unstable detrusor function found in this group of patients is by no means confined to enuretics, but most enuretics with this type of detrusor instability usually have diurnal frequency and nocturia—whether they wet their beds or not is incidental and relates to their depth of sleep pattern (Whiteside and Turner-Warwick, 1979).

It was virtually impossible to find patients in Groups III and IV who had never taken drugs for their bladder symptoms and 11 patients had also undergone a Helmstein's distension (Helmstein, 1972). However, in previous work in this

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department neither the drugs in use (Farrar and Osborne, 1976) nor bladder distension (Pengelly *et al.*, 1978) had been shown to have any significant effects on cystometry, so these patients were included.

Results were studied under 2 main headings: the filling cystometrogram and the voiding characteristics.

The Filling Cystometrogram

The following measurements were recorded:

1. The bladder capacity.
2. The maximum intrinsic detrusor pressure (IDP) during filling in the supine and/or erect positions.
3. Any rise in the supine intrinsic detrusor pressure (IDP) on tilting to the erect position with a full bladder (Arnold, 1974).
4. Any rise in intrinsic detrusor pressure (IDP) initiated by coughing—"cough trigger instability".

A rise in the IDP above 15 cm H_2O during these provocative tests was regarded as evidence of detrusor instability.

The Voiding Characteristics

The following measurements were recorded:

1. The peak urinary flow (PUF) rate, which we consider should be greater than 17 ml/s with a voided volume of at least 250 ml.
2. The intrinsic detrusor pressure (IDP) during the period of peak urinary flow (PUF), which we consider should be below 50 cm H_2O in women and 60 cm H_2O in men.
3. The residual urine after voiding in private.

Results

All patients, except 4 of the enuretics from Group IV, had at least 2 technically satisfactory cystometrograms but accurate voiding data were not available from 16 patients, all females, who were unable to void satisfactorily "in public" during the routine test; if a patient had already produced a satisfactory free flow rate whilst voiding in private into a uroflowmeter, further attempts to obtain voiding studies were not always undertaken during videocystography unless they were felt likely to provide further information of relevance to the patient's clinical problem. There are therefore fewer accurate voiding records available for study than filling cystometrograms.

The PUF rate measured during a synchronous study may or may not be representative of the patient's free flow rate. In general, a PUF exceeding about 17 ml/s under the circumstances of examination can be regarded as normal provided the voiding pressure is not elevated. However, a PUF much less than this must always be ignored in favour of one recorded during voiding in privacy. Voluntary contraction of the distal sphincter caused by embarrassment or by voiding in an unnatural posture can forcefully raise the IDP and lower the PUF—especially in the female.

Group I Nineteen urodynamically normal, though not necessarily asymptomatic, patients underwent 41 videocystograms (Table 1). In all patients the IDP never rose above 15 cm H_2O during filling, standing, filling erect, or coughing at any examination.

During voiding the PUF never varied by more than 3 ml/s and the IDP difference between consecutive voids was never greater than 10 cm H_2O in 11 of the 13 patients with technically satisfactory voiding performances. All of the patients voided to completion, leaving no residual urine on each occasion.

Table 1 Patient Groups

Group	*Videocystogram diagnosis*	*Patients*				*Number of video-cystograms*
		Ages	*Male*	*Female*	*Total*	
I	Normal	7-72	4	15	19	41
II	Stable stress incontinence	24-74	0	4	4	8
III	Idiopathic detrusor instability	38-76	1	24	25	56
IV	Enuretic or exenuretic instability	11-52	5	11	16	40
Total		7-76	10	54	64	145

Table 2 Cystometry and Voiding Characteristics of Patients with Stable Bladders: Groups I and II

Cystometry	*Group I*	*Group II*
	19 patients, 41 videos	*4 patients, 8 videos*
Mean bladder capacity	476 ml; range 180-700 ml	466 ml; range 300-700 ml
Maximum difference between consecutive fills	270 ml	150 ml
Mean difference between consecutive fills	70 ml	93 ml
IDP rise during:		
filling standing coughing	<15 cm H_2O; 19 pts all videos	<15 cm H_2O; 4 pts all videos
Voiding characteristics	*13 patients, 26 videos*	*3 patients, 6 videos*
PUF at consecutive voids	Identical: 8 pts Diff. 1-3 ml/s: 5 pts	Identical: 3pts
IDP at PUF in consecutive voids	Identical: 5 pts Diff. 1-10 cm H_2O: 6 pts Diff. 11-15 cm H_2O: 2 pts	Identical: 3 pts

Group II Four female patients who had stable bladders and simple stress incontinence were each studied twice (Table 2). All of the patients had stable bladders on provocative testing and the PUFs and IDP were identical on each occasion. The voiding part of the examination was performed satisfactorily in 3 out of the 4 patients in the group.

Group III Twenty-five patients with idiopathic detrusor instability underwent 56 videocystograms (Table 3). The difference in the maximum IDP between consecutive filling cystometrograms in the same patient was 15 cm H_2O or less in 18 of the 25 patients, between 16 and 40 cm H_2O in 5, with only 2 patients having a stable filling cystometrogram at one examination but an unstable cystometrogram at the next examination. The response to standing was much more variable, with 8 patients having a rise in IDP at each examination and 8 having an inconstant rise. The voiding characteristics correlated very closely, the differences in PUF never exceeding 6 ml/s in any patient and the differences in IDP at PUF by 10 cm H_2O or less in 17 of the 18 patients studied who were able to void satisfactorily.

Group IV Sixteen patients with unstable bladders and a history of prolonged childhood or lifelong enuresis were studied (Table 3). Twelve patients had 25 filling cystometrograms suitable for study and in 9 patients the IDP difference on

Table 3 Cystometry and Voiding Characteristics of Patients with Unstable Bladders: Groups III and IV

Cystometry	*Group III*	*Group IV*
	25 patients, 56 videos	*12 patients, 25 videos*
Mean bladder capacity	409 ml; range 200-750 ml	402 ml; range 200-660 ml
Maximum difference between consecutive fills	450 ml	240 ml
Mean difference between consecutive fills	72 ml	71 ml
IDP difference between consecutive fills	Identical: 12 pts	Identical: 4 pts
	1-15 cm H_2O: 6 pts	1-15 cm H_2O: 5 pts
	16-40 cm H_2O: 5 pts	16-25 cm H_2O: 2 pts
Stable one fill; unstable another fill	: 2 pts	: 1 pt
	25 pts	12 pts
Voiding characteristics	*18 patients, 36 videos*	*14 patients, 34 videos*
PUF at consecutive voids	Identical: 8 pts Diff. 1-6 ml/s: 10 pts	Identical: 7 pts Diff. 1-6 ml/s: 7 pts
IDP at PUF in consecutive voids	Identical: 4 pts Diff. 1-10 cm H_2O: 13 pts Diff. 11-15 cm H_2O: 1 pt	Identical: 7 pts Diff. 1-10 cm H_2O: 3 pts Diff. 11-25 cm H_2O: 4 pts

filling varied by 15 cm H_2O or less, between 16 and 25 cm H_2O in 2 patients, and in 1 patient the cystometrogram was stable at the first but unstable at the second examination. IDP rises were inconstant on standing and coughing, as in Group III. Voiding PUF rates correlated very closely, the differences never exceeding 6 ml/s and the IDP at PUF varied by 10 cm H_2O or less in 10 of the 14 patients studied who were able to void satisfactorily.

Discussion

The Filling Cystometrogram

1. *The Filling Volume* This is not an accurate method of determining the true bladder capacity owing to variations in the subjective response of the conscious patient under the circumstances of the test, as evidenced by the figures giving the greatest difference between consecutive filling volumes in the same patient. The average capacity of all of the unstable bladders (Groups III and IV) is lower than that of the stable bladders (Groups I and II) but the difference is small—406 to 449 ml respectively.

2. *IDP During Filling* This remained below 15 cm H_2O at all times in all Group I and II patients. In the 37 patients in Groups III and IV with unstable filling cystometrograms, the IDP rise was identical or varied by no more than 15 cm H_2O between consecutive examinations in 27 patients (73%). In 7 the pressures varied from 20 to 35 cm H_2O (19%), and in only 3 patients (8%) was the cystometrogram stable at one examination but unstable at the next. In all 4 groups combined the filling cystometrogram was qualitatively the same in 57 of the 60 patients (95%) with satisfactory cystometrograms.

3. *IDP Rise on Standing* This occurred in 21 patients, but was constant at each examination in only 12 (57%) and therefore seemed to be an inconsistent response.

4. *IDP Rise on Coughing* Cough trigger instability was seen in 3 patients, but was constant in only one and seemed also to be an inconsistent response.

These results demonstrated that provocative liquid fill cystometry was a test with a high degree of accuracy in the diagnosis of detrusor instability and that the qualitative results remained consistent in 92% of our unstable cases, even over a period of several years. However, although 73% of these unstable cases had quantitatively highly reproducible unstable IDP rises during filling cystometry, 27% had IDP rises differing by more than 15 cm H_2O between consecutive fills. This quantitative discrepancy of 27% compared exactly with the results obtained by Wein *et al.* (1978) using gas fill cystometry at 100 ml/min repeated on consecutive days in 20 apparently normal men. Therefore we feel that great care must be exercised in interpreting the significance of pressure changes when filling cystometry is used for the objective assessment of therapy for detrusor instability.

The Micturition Characteristics

Forty-eight of the 64 patients had at least 2 micturition recordings suitable for comparison.

When correctly assessed, the voiding flow pattern of a patient was highly reproducible, with the PUF varying by not more than 5 ml/s in 44/48 patients (92%) and by only 6 to 7 ml/s in the remaining 4. Similarly, the IDP during PUF varied by not more than 15 cm H_2O in 44/48 patients (92%).

The mean voiding pressure in the patients from Groups I, II and III combined was 42 cm H_2O, but in the Group IV patients with instability associated with a history of enuresis it was 59 cm H_2O. This suggests that enuretic patients void with higher pressures than those usually seen in the absence of outflow obstruction. They also characteristically have very powerful bladder after-contractions at the end of micturition.

It is concluded that synchronous combined pressure/flow videocystography is a highly reproducible method of assessing bladder dynamics. In the relatively static conditions studied here the cystometry of an individual patient's bladder remained qualitatively constant after a long period in 95% of all of the patients examined, and in 92% of those patients with detrusor instability.

In 73% of patients who developed unstable IDP rises during filling cystometry, the pressure rises remained the same or very similar, even when a number of years separated the examinations; micturition characteristics were even more constant.

Therefore, provided due care is taken, it is justifiable to draw reasonable *qualitative* deductions from comparative studies in the same patient, even when the interval between examinations is considerable. However, more care must be exercised when interpreting individual *quantitative* recordings.

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The Relation of Urinary Bilharziasis to Vesical Stones in Children

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Summary—Of 64 children in Khartoum with vesical stones only one had urinary bilharziasis. Bilharziasis appears to play no part in the development of these stones, which probably have the same aetiology as stones in other endemic areas.

Both urinary bilharziasis and vesical stones in children are common in the Sudan: Most children with stones come from rural areas where urinary bilharziasis is endemic. It is known that bilharzial infestation of the bladder may predispose to vesical stones (Makar, 1955). It was therefore decided to investigate the role of bilharziasis in the aetiology of vesical stones in children.

Patients and Methods

Sixty-four consecutive male children with vesical stones were investigated. Their mean age was 4.2 years (range 1-4 years). All but 4 came from areas where bilharziasis was endemic. None had a past history of bilharziasis. The following investigations were performed:

(1) Daily examination of urine for bilharzia ova for 7 days. (2) Examination of the centrifuged deposit of a 24-h specimen of urine for ova. (3) Intravenous urography. (4) Cystoscopy. During the examination at least 3 mucosal biopsies were taken from the trigone or other areas showing evidence of inflammation. (5) At operation (vesicolithotomy) a full thickness biopsy was taken from the anterior bladder wall.

Results and Discussion

Intravenous urography revealed no abnormality of the urinary tract, except for the stone, in any of the patients.

Repeated examination of urine revealed the presence of schistosoma haematobium ova in only one patient, a boy of 13 years. In the same patient ova were also present in the cystoscopic and bladder wall biopsies.

In the remaining 63 patients repeated examination of urine, cystoscopic and bladder wall biopsies were all negative for ova. The cystoscopic appearance was normal, except for the stone, in 12 patients; there were various degrees of cystitis in the remainder. Histopathological examination showed no abnormality in the bladder in 5 and non-specific inflammation in 58 children. One child was reported as having bilharzial cystitis with numerous ova.

These results indicate that urinary bilharziasis plays no role in the aetiology of vesical stones in children in Khartoum. Similar results were reported from Egypt, where investigation of 50 children with vesical stones revealed no evidence of urinary bilharziasis (Lutfi *et al.*, 1974).

In Khartoum, although urinary bilharziasis may affect very young children (Omer, 1978; personal communication), it seems that the infestation occurs mostly in older children and young adults.

Not uncommonly we see older patients with both urinary bilharziasis and vesical stones. We believe that bilharziasis may predispose to vesical stones when it causes bladder neck stenosis. In this event the stone usually recurs following lithotomy unless the bladder neck stenosis is corrected. On the other hand, vesical stones in children are not usually associated with any abnormality of the urinary tract and they rarely recur after removal.

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Vesical Leukoplakia Progressing to Squamous Cell Carcinoma in Women

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Summary—A series of 13 women and 4 men with vesical leukoplakia is presented. Three of the women progressed to squamous cell carcinoma. Early diagnosis of malignant change is difficult and prophylactic cystectomy for persistent widespread vesical leukoplakia may be justifiable in both sexes.

Although Rokitansky described vesical leukoplakia in 1861, we remain ignorant of the aetiology and unable either to cure it in its generalised form or to prevent it from progressing to squamous cell carcinoma. For many years it has been recognised that leukoplakia is a pre-malignant condition and 7 cases of men with vesical leukoplakia developing carcinoma have been reported in the literature; as far as we are aware, however, no similar case has been reported in women and for this reason some people believe that the condition is less serious in them. The purpose of this paper is to report, for the first time, 3 women with vesical leukoplakia which progressed to squamous cell carcinoma while having regular follow-up cystoscopic examination.

Patients

Between October 1968 and December 1979, 17 cases of histologically proven vesical leukoplakia were seen in the Department of Urology, General Infirmary, Leeds. Thirteen of these patients were female and 4 male; 6 females had widespread vesical lesions. The mean age at the time of diagnosis was 56 years. The average duration of follow-up was 6.8 years (range 6 months to 14 years). The management of these patients was as follows: treatment of urinary infection with antibiotics; acidification of the urine with Mandelamine (Warner) and ascorbic acid; cystoscopy every 6 months, with biopsy of areas where carcinoma was suspected.

While having regular follow-up by cystoscopy, 3 women progressed to squamous cell carcinoma. All of them had extensive vesical leukoplakia.

Case Reports

Case 1. A 65-year-old woman, who previously had had a right nephrectomy for stones, presented with increased frequency of micturition and urinary infection. At cystoscopy a diagnosis of vesical leukoplakia was made and was subsequently confirmed by histological examination of a biopsy. Her urinary infection was treated, her urine was acidified and she was followed up by regular cystoscopy. Five years after diagnosis she developed an invasive squamous cell carcinoma for which she had a urinary diversion as the first stage of a planned 2-stage cystectomy. After this she developed pain in her hip and radiography showed a metastasis. Her condition rapidly deteriorated and within 4 months of the diagnosis of the carcinoma she had died of widespread disease.

Case 2. A 67-year-old woman with disseminated sclerosis presented with acute retention of urine. An intravenous urogram showed an atonic bladder. Cystoscopy showed the typical appearance of widespread leukoplakia. This was confirmed histologically in 3 separate biopsies, each of which showed no evidence of carcinoma. Associated urinary tract infection was treated promptly and followed by long-term acidification of her urine. At her first check cystoscopy 6 months later an ulcerated area was seen in the base of the bladder and biopsy showed that this was an invasive squamous cell carcinoma. A chest X-ray and skeletal scan showed no distant spread and the patient was treated by radical cystectomy and urinary diversion.

Case 3. A 67-year-old woman presented with right loin pain and increased frequency of micturition; on examination she had an enlarged bladder. She gave a history of a previous operation on her left ureter for stone. An intravenous urogram showed a non-functioning kidney

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on the left and chronic pyelonephritis on the right. At cystoscopy urethral stenosis, areas of leukoplakia and gaping ureteric orifices were found. The diagnosis of leukoplakia was confirmed by biopsies and a micturating cystogram showed bilateral ureteric reflux. Left nephroureterectomy was performed together with reimplantation of the right ureter. She was followed up by repeated urethral dilatation and check cystoscopy; her urine was acidified and on many occasions she required courses of antibiotics for recurrent urinary infection. On several occasions biopsy showed leukoplakia without evidence of carcinoma. Seven years after the original diagnosis of leukoplakia a reddened area was seen in the fundus of the bladder on cystoscopy; biopsy showed poorly differentiated squamous cell carcinoma. After chest X-ray and bone scan had shown no evidence of metastases, a urinary diversion was performed as the first stage of a planned 2-stage cystectomy.

Discussion

In 1953 McDonald described vesical leukoplakia as the cornification of a non-cornifying membrane. This is thought by most pathologists to be produced by metaplasia of the transitional cells.

In most of the series of vesical leukoplakia reported in the literature there is a 4:1 male preponderance (Reece and Koontz, 1975). The only series showing a female preponderance is that reported in 1956 by Abeshouse and Tankin. The present study also shows a female preponderance.

It is necessary to differentiate between cases of squamous cell carcinoma of the bladder associated with vesical leukoplakia and cases of histologically proven leukoplakia which while under observation have progressed to squamous cell carcinoma. In 1961 Holley and Mellinger reported the first such case and in 1963 Kelalis *et al.* reported a similar case. O'Flynn and Mullaney in 1974 reported a further 5 cases in a series of 20 patients with leukoplakia. All 7 patients were male. Our present paper is the first report of women with vesical leukoplakia progressing to squamous cell carcinoma and it shows a similar incidence of malignant change. The widely accepted pre-malignant character of vesical leukoplakia is thus not restricted to males only.

Treatment of vesical leukoplakia is still unsatisfactory. While small, localised lesions may be resected transurethrally, no treatment has yet been effective for widespread lesions. Symptoms are of little help in diagnosing malignant change, and even repeated cystoscopy and biopsy may fail to do so because the tumour may be hidden beneath the plaque of keratin. By the time the tumour is diagnosed it may already be too far advanced for the patient to be cured by cystectomy. For this reason prophylactic cystectomy may be justifiable in both men and women with widespread vesical leukoplakia.

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Combined Chemotherapy in the Management of Metastatic Bladder Cancer

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Summary—In a non-randomised study, 30 patients with metastatic bladder cancer were treated with a combination of Adriamycin, VM 26, 5-fluorouracil (5-FU) and mitomycin C. A significant response was observed in 18 patients and the median survival was 300 days.

Cancer of the bladder ranks among the common causes of death from cancer in males. It is a disease of elderly men and the incidence is about 3 times higher in males than in females.

Classical treatment includes surgery and radiotherapy. These local forms of treatment appear to be less than adequate, however, for even when tumour infiltration is less than half-way through the bladder wall, metastases are observed in about 40% of patients; furthermore, when the perivesical fat is affected, most of these tumours have already metastasised.

When metastases appear, life expectancy is very short and is not necessarily related to the evolution of the original bladder tumour. The poor prognosis in bladder cancer would seem to justify the more frequent use of adjuvant chemotherapy, although combined chemotherapy trials in advanced bladder carcinoma have so far produced only temporary benefit (Murphy, 1977; Steinberg *et al.*, 1977; Whitmore, 1979).

The aim of this phase II trial was to study the activity of a combination of 4 drugs for the management of advanced metastatic bladder cancer. The trial was not randomised and was limited to patients under 70 years of age with metastatic bladder cancer; they all received chemotherapy and local palliative treatment.

Patients and Methods

Between April 1976 and December 1978, 30 patients with T2 to T4 bladder carcinoma were studied; they all had measurable lesions detected by clinical, cystoscopic and radiological examination before the start of treatment.

All patients had metastases (bone 47%; lung 43%) and one of the following characteristics: (*a*) T2 to T4 tumours treated by surgery, radiotherapy or both; (*b*) residual or recurrent cancer after surgery; (*c*) positive distant lymph nodes.

Physical examination, performance status (Karnofsky scale), full blood count, blood urea, serum creatinine, urine analysis, cystoscopy with biopsy, chest X-ray, intravenous urography and cystography, bone scanning and bidimensional tumour measurement were recorded.

The variations in response were due to the modification of measurable metastases. We did not include any differences observed in the bladder lesion.

Patients received a 5-day course of treatment with Adriamycin (40 mg/m^2) on day 1, VM 26 (60 mg/m^2) on days 2 and 3, 5-FU (500 mg/m^2) on days 4 and 5, and mitomycin C (10 mg/m^2) on day 4. This was administered once a month for 10 consecutive months and was then continued without Adriamycin.

All patients were given treatment as required to prevent and control pain and urinary obstruction.

Results

The results of treatment with this combination of drugs (AVFM) are shown in the Table. The treatment was generally well tolerated but caused alopecia and vomiting, and leucopenia often occurred after the third cycle. Only one patient achieved a complete response. Patients achieving objective responses always showed a reduction in their clinical symptoms, and in particular a lessening of bone pain.

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Table Results of Chemotherapy in 30 Patients With Metastatic Bladder Carcinoma

	Number of patients
Complete remission	1 (3%)
<50%	13 (45%)
>50%	4 (13%)
Stabilisation	2 (7%)
Failure	9 (30%)
Not interpretable	1 (3%)
Total	30

Discussion

Several protocols have been used in an attempt to assess the effectiveness of chemotherapy in invasive bladder cancer (Steinberg *et al.*, 1977; Valeriote and Edelstein, 1977; Carter, 1978). Yagoda (1977) obtained a 26% response rate using a combination of cyclophosphamide and Adriamycin and Cross *et al.* (1976) achieved a 35% response rate with 5-FU and Adriamycin.

The survival of patients treated with the AVFM regimen is shown in the Figure. Length of survival was measured from the time that metastases appeared and was independent of regional treatment of the bladder tumour. The size of the primary tumour did not appear to correlate with the appearance of metastases, and the occurrence of metastases often indicated a poor prognosis. The mean survival time was 10 months and 30% of patients were still alive after one year. We did not observe a plateau.

With regard to previously treated primary tumours, we found merely a correlation between the incidence of regression of metastases and regression of the bladder tumour.

There are at least 3 factors which could explain why the response to chemotherapy of primary bladder carcinoma is inferior to that of metastatic cancer: (*a*) a primary tumour will often have undergone irradiation either as initial treatment or following recurrence; (*b*) it is often a slow-growing tumour with very few dividing cells; (*c*) vascularisation may have been greatly altered by surgery and/or irradiation. On the other hand, metastases are likely to have a high growth level and a good vascular base to enhance the action of chemotherapeutic compounds.

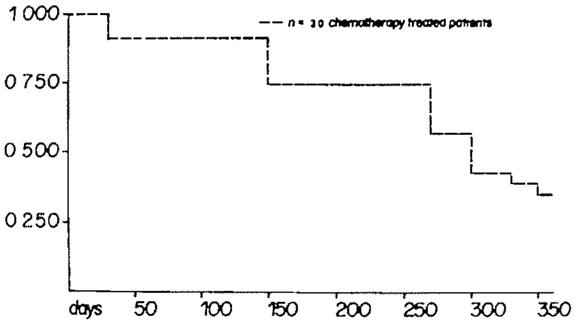

Fig. The survival of metastatic bladder carcinoma patients treated with chemotherapy.

Although it is difficult to draw conclusions from a non-randomised clinical trial, our results suggest that this combination of drugs is partially effective for metastases but has no obvious effect on the spread of the primary tumour.

The association of local and systemic chemotherapy may modify this picture.

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Single-Drug Chemotherapy with 5-FU and Adriamycin in Metastatic Bladder Carcinoma

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Summary—Either 5-fluorouracil (5-FU) or Adriamycin was used as single-drug treatment in 10 and 15 patients respectively with measurable metastatic bladder carcinoma. In the 5-FU group there were one complete and 2 partial remissions. Six partial remissions were observed in patients treated with Adriamycin. The duration of the remissions was usually short. Gastrointestinal and haematological side effects were more pronounced in the Adriamycin group. The results are discussed in relation to other reports on cytostatic treatment of bladder carcinoma, with emphasis on general problems concerning chemotherapy of this disease.

Carcinoma of the urinary bladder is only moderately sensitive to the known cytostatic drugs. Furthermore, the response rates differ widely in the various reports (deKernion, 1977; Yagoda, 1977). This probably reflects variations in dose schedules and different methods of evaluating response. Another problem concerning the chemotherapy of bladder carcinoma is that the number of patients with measurable disease is limited. Furthermore, because of their age and poor general condition, not all such patients are suitable for a clinical study.

From 1972 to 1976 5-FU was used in patients with metastatic bladder cancer admitted to The Norwegian Radium Hospital. From 1976 to 1978 such patients were treated with Adriamycin. In this retrospective study, our experience with these 2 drugs is reported.

Patients and Methods

5-FU (12 mg/kg body weight) was given intravenously at weekly intervals to 10 patients with measurable metastatic bladder carcinoma as initial treatment after the diagnosis of metastatic disease. Adriamycin (75 mg/m^2 body surface intravenously, repeated at 3-week intervals) was used in 15 comparable patients with metastatic bladder carcinoma. Only patients with lung metastases, external lymph node metastases, and/or subcutaneous metastases were included in this study. Eight patients treated with 5-FU had lung metastases. Two of these patients also had external lymph node metastases. Subcutaneous metastases were found in 2 patients in the 5-FU group. All of the Adriamycin-treated patients presented with lung metastases. The degree of histological differentiation of the primary tumour was evaluated according to the WHO classification (Mostofi *et al.*, 1973). In the 5-FU group, grade III was found in 7 patients and 3 had an undifferentiated bladder tumour. Five patients treated with Adriamycin had a grade II bladder carcinoma. In 9 patients in the Adriamycin group grade III was found, whereas one patient had an undifferentiated primary tumour.

The patients' ages ranged from 51 to 78 years. The Karnofsky index was above 70 in all cases.

In all patients the size of the primary tumour was evaluated prior to the start and at the end of chemotherapy by cystoscopic examination and/or rectal palpation under general anaesthesia (UICC, 1974). Prior to chemotherapy, 7 patients in the 5-FU group and 9 patients treated with Adriamycin had been given a full course of high voltage irradiation (60 Gray) to the true pelvis. It is often impossible to distinguish between category T2 and T3 in previously operated and/or irradiated patients. Therefore these categories were grouped together: category T2/T3. The distribution of the T categories was as follows: 5-FU group: T0 (after total cystectomy)—1 patient; T1—1 patient; T2/T3—2 patients; T4—6 patients; Adriamycin group: T0 (after total cystectomy)—1 patient; T1—2 patients; T2/T3—7 patients; T4—5 patients.

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Evaluation of Response The largest perpendicular diameters of the metastases were measured before and after chemotherapy. *Complete remission* was defined as the disappearance of all evidence of tumour. *Partial remission* implied a ≥50% decrease of the sum of the products of the 2 diameters, provided that there was no evidence of new tumour and no progression of any previous lesions. The definition of *stable disease* was a <50% decrease or <25% increase of the sum of the products of the 2 diameters with no new tumour. Any sign of new lesions, mixed response, or an increase of the sum of the products of the 2 diameters by ≥25% was taken as *progression*. No fixed period of time for complete or partial remission was defined. The duration of the remissions was calculated from the start of chemotherapy to the first sign of progressive disease. If the disease showed progression after at least 6 to 8 weeks' treatment, chemotherapy was discontinued. If stable disease or complete/partial remission was found after 6 to 8 weeks' chemotherapy, cytostatic treatment was continued until progression, provided that no major toxic side effects were observed.

We found it very difficult to devise reliable definitions for the evaluation of the primary tumour, especially after previous irradiation to the true pelvis. We decided therefore to define only complete remission of the primary tumour, *i.e.* the return to normal of all findings by cystoscopy and/or rectal palpation, histological proof of disappearance of the primary tumour, and normal urinary cytology. If these conditions were not fulfilled, we stated only that there was cystoscopic and/or palpable tumour in the true pelvis or in the bladder at the start and at the end of chemotherapy.

Results

Response (Table 1) Among the 10 patients treated with 5-FU one complete and 2 partial remissions were observed. The complete remission lasted for 63 months. This patient was treated for 3 years with 5-FU injections weekly because of a histologically proven undifferentiated bladder carcinoma with cytologically verified subcutaneous metastases to the penis. Six months after the start of treatment, cystoscopy and rectal exploration showed no evidence of disease. Malignancy could not be demonstrated in biopsies taken by transurethral resection from the previous tumour bed. The subcutaneous nodules in the penis had disappeared. After discontinuation of 5-FU no recurrence of either the bladder tumour or the subcutaneous metastases was observed. The patient died, still in complete remission from his bladder cancer, from gastric carcinoma 27 months after discontinuation of 5-FU. An autopsy was not performed.

Table 1 Response to 5-FU or Adriamycin in Patients with Measurable Metastatic Bladder Carcinoma

	5-FU (10 patients)	*Adriamycin (15 patients)*
Complete remission	1 (63)*	0
Partial remission	2 (2, 3)*	6 (5, 4, 2, 4, 4, 3)*
Stable disease	2	5
Progression	5	4

* Duration of remission in months.

There were 6 partial remissions of lung metastases among 15 patients treated with Adriamycin. In patients with objective remissions, the reduction of lung metastases could be observed 3 weeks after the first injection of Adriamycin. If the metastases did not show reduction after 6 weeks' chemotherapy, further treatment did not result in a subsequent remission. As a rule, remissions lasted for only 2 to 5 months.

The frequency of remissions could not be related to the histological grade of the primary tumour. Except for the complete remission in the 5-FU group, the size of the primary tumour remained unchanged during chemotherapy with both drugs. In the present study, chemotherapy did not seem to reduce the symptoms caused by the primary tumour (frequency, dysuria, pelvic pain).

Table 2 Side Effects of Single Drug Treatment with 5-FU or Adriamycin in Patients with Metastatic Bladder Carcinoma

	5-FU (10 patients)	*Adriamycin (15 patients)*
Gastrointestinal		
Nausea	2	15
Vomiting	0	13 (1 severe)
Diarrhoea	3	1
Haematological		
Leukopenia <2.0 × 10^9/l	2	9
Thrombocytopenia <100 × 10^9/l	0	1
Alopecia	0	15
Cardiac failure	0	0
Skin necrosis (due to extravasation at site of injection)	0	1

Side effects (Table 2) All side effects, including gastrointestinal symptoms, were observed more often in patients treated with Adriamycin than with 5-FU. Vomiting and severe nausea usually disappeared within 4 days after the injection of Adriamycin. In one patient, however, vomiting was severe and prolonged and further treatment was refused after 2 injections. One patient developed a severe skin and muscle necrosis of the forearm due to extravasation of Adriamycin at the site of injection.

In this retrospective study it was difficult to evaluate the quality of life and the palliative effect in bladder carcinoma patients receiving chemotherapy. Treatment with 5-FU as a single drug did not seem to have a significant influence on their quality of life. All patients were treated with 5-FU as out-patients, but treatment with Adriamycin caused a higher degree of morbidity and most patients were kept in hospital for a few days.

Discussion

This retrospective study was undertaken in order to analyse the effect of 5-FU and Adriamycin on patients with metastatic transitional cell carcinoma from the urinary bladder. In the literature, the response rates obtained by these and other cytostatic drugs vary to a marked degree (Carter and Wasserman, 1975; deKernion, 1977; Yagoda, 1977). This may reflect the difficulties that oncologists have in evaluating response in this group. It is often impossible to evaluate the effect of chemotherapy on the primary tumour if the patient has previously received a full course of radiotherapy or is operated upon several times prior to cytostatic treatment. Post-irradiation fibrosis or post-operative changes in the true pelvis may be impossible to differentiate from tumour infiltration. Tumour manifestations, evaluable by exact measurements (*e.g.* subcutaneous metastases or lung metastases), are relatively uncommon in metastatic bladder carcinoma. Furthermore, it is difficult to assess the response of metastatic lesions in bone, liver and peritoneum, or in lymph nodes when shown only lymphographically. New diagnostic methods have been developed to measure tumour and metastatic size (ultrasound, scintigraphic methods, computer tomography). However, their role in defining partial remission, for example, is still under investigation.

In this study we included only patients with metastases that were easily measurable by clinical and/or radiological examination. The discovery of any new metastasis was regarded as progression, even if it was not strictly measurable.

The role of 5-FU in bladder carcinoma is not clear. In a review, deKernion (1977) reported an objective response rate of 39% (range 0-75%). The fact that we found 3 responders among 10 patients treated with 5-FU as a single drug confirms that it has some effect in bladder carcinoma. Weekly injections of 5-FU are easily administered and the drug is well tolerated even by older patients. Our study indicates that 5-FU should be used in some of those patients in whom chemotherapy is considered. The drug should be used particularly in patients who are not expected to tolerate treatment with more toxic drugs.

It is concluded that Adriamycin in adequate doses also seems to be an effective cytostatic drug in metastatic bladder cancer, since 6 out of 15 patients achieved a partial remission. These results are in agreement with the response rates reported by Carter and Wasserman (1975). They are, however, at variance with more recent observations (Yagoda *et al.*, 1977; Turner *et al.*, 1979), possibly depending on differences between the dosages used and the patient groups.

Only drugs which have shown a cytostatic effect when used singly should be used together. Using a combination of 5-FU and Adriamycin, some authors have obtained objective remission rates ranging between 35 and 40% in bladder carcinoma (Cross *et al.*, 1976; EORTC Urological Group B, 1977). It would seem therefore that they are no more effective when used together than when used singly, and this reflects the need for randomised clinical studies to compare single-drug treatment with combination drug chemotherapy in metastatic bladder carcinoma.

Except for the patient with complete remission after treatment with 5-FU, the duration of the remissions was relatively short for both drugs when used singly. It is therefore doubtful how far such chemotherapy significantly prolongs survival in most of these patients with measurable metastatic bladder carcinoma, and in evaluating the role of chemotherapy increasing consideration should be given to other effects such as the patient's performance status and any decrease in pain.

This study supports the view that bladder cancer is only moderately sensitive to conventional chemotherapy. New cytostatic drugs, *e.g.*

cis-platinum (Merrin, 1978; Yagoda *et al.*, 1978) or drug combinations (Sternberg *et al.*, 1977), may increase the response rates but they also increase morbidity in these relatively old patients. It is not yet known what parameters will predict the response to chemotherapy and the degree of morbidity in individual patients and most of these patients, when treated with drugs, will receive a more or less toxic form of treatment with very limited benefit, if any.

Nevertheless, we have found that chemotherapy is worth trying, especially in those with measurable disease where the response can be evaluated properly. Only by such trials is it possible to define the most effective treatment, although the response rates should always be considered in relation to side effects and morbidity.

This study also indicates that one hospital seldom has enough patients to assess the real value of cytostatic therapy in bladder carcinoma within a reasonable time. New drugs and drug combinations are continually being developed, however, and clinical trials are highly desirable. For current forms of chemotherapy to be assessed reasonably quickly, patients should enter cooperative phase II studies which should be based on well defined protocols where measurable tumours are used for the evaluation of response.

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Urinary Protein Profiles in Patients with Urothelial Bladder Tumours

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Summary—Urinary protein profiles were studied in 32 patients with urothelial bladder tumours, using immunonephelometry. In patients with and without residual or recurrent tumours a glomerular type of proteinuria was demonstrated. In patients with grade III-IV transitional cell carcinoma the glomerular proteinuria was more severe than in patients with grade I-II tumours. Increased excretion of low molecular weight proteins was observed only in patients with grade III-IV tumours.

The use of the increased relative clearance of albumin, transferrin, and haptoglobin as a diagnostic test was attempted in detecting residual or recurrent tumours. In patients with grade III-IV tumours the predictive value of a positive or negative test was 92% and 100% respectively, whereas the relative protein clearance was without predictive value in patients with grade I-II tumours.

Increased urinary protein excretion is a common finding in patients with neoplastic disease of the kidney or urinary tract (Harvey, 1947; Johansson *et al.*, 1971; Hemmingsen and Skaarup, 1977a). In connection with urothelial tumours, urinary protein excretion has been studied extensively (Johansson and Ljungquist, 1974; Johansson, 1975; Johansson and Kistner, 1975). However, an evaluation of urinary protein excretion in patients with bladder tumours compared with protein excretion in apparently healthy subjects, and studies dealing with the urinary excretion of low molecular weight plasma proteins in patients with bladder tumours, have not been reported.

The aim of the present study was to investigate urinary excretion and renal clearance of 9 plasma proteins in patients with urothelial bladder tumours, to correlate the degree of differentiation of the urothelial lesion to protein excretion, and to evaluate the possible predictive value of increased urinary protein excretion in detecting residual or recurrent tumours after primary treatment and dissemination of the tumour.

Materials and Methods

Thirty-one patients with transitional cell carcinoma of the urinary bladder were studied. There were 23 men and 8 women, aged from 42 to 79 years. Two hundred and twenty-one apparently healthy subjects were included as control subjects (Hemmingsen and Skaarup, 1975).

The diagnosis of the bladder tumours was confirmed by histological examination of biopsy or resection specimens. Fifteen patients had grade I-II and 16 patients grade III-IV transitional cell carcinoma of the urinary bladder (Bergkvist *et al.*, 1965). Distant metastases were demonstrated in 5 patients with grade III or IV tumours. Patients with grade I or II tumours were treated by either transurethral or transvesical resection. Fourteen of the patients with grade III or IV tumours received radiotherapy, in one case followed by cystectomy and urinary diversion. The remaining 2 patients were treated by tumour resection.

Twenty-seven of the patients with transitional cell carcinoma were available for further sequential studies, with cystoscopy and urinary protein determinations being performed simultaneously. The presence of tumour was confirmed by histological examination of the biopsy specimen. Finally, one patient with squamous cell carcinoma of the urinary bladder was studied sequentially. This patient was treated by cystectomy and urinary diversion.

Urinary protein determinations were started at cystoscopy 3 months after primary treatment, since almost all patients before treatment showed

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severe urinary blood contamination which would invalidate protein determination (Hemmingsen and Skaarup, 1977a).

At each of 103 examinations a 24-h urine and a blood sample were collected. The samples were kept below +4°C without addition of preservatives, until protein analysis could be carried out.

The urinary sediment showed either total absence or insignificant numbers of erythrocytes, leucocytes, bacteria or casts, and the pH of all urine samples was above 5.5. The urinary and serum creatinine concentrations were determined by Jaffé's reaction (Auto-Analyzer^R). All patients had a normal creatinine clearance related to age, sex and body surface during the study (Kampmann *et al.*, 1971).

The determination of specific proteins in urine and serum was performed by immunonephelometry. The method has been described in detail elsewhere (Skaarup, 1978). The proteins studied were 6 of high molecular weight: albumin, transferrin, haptoglobin, IgG, IgA and IgM for evaluation of the glomerular type of proteinuria, and 3 of low molecular weight: free light λ and $\varkappa$ chains of immunoglobulin and β_2-microglobulin for evaluation of the tubular type of proteinuria (Hardwicke, 1975). The proteins were measured as protein-related material, since some of them could be present in the urine either as whole molecules, aggregated, or split products with preserved antigenic determinants (Hermann *et al.*, 1970; Peterson and Berggård, 1971; Wadsworth, 1976).

The relative clearance of the high molecular weight proteins was calculated by the formula $(U_p \,.\, V/S_p) / (U_{Cr} \,.\, V/S_{Cr})$ and the relative excretion of the low molecular weight proteins by the formula $(U_p \,.\, V) / (U_{Cr} \,.\, V/S_{Cr})$, where U_p and S_p denote the urinary and serum concentration of the specific protein, U_{Cr} and S_{Cr} the urinary and serum concentration of creatinine, and V the urine volume per unit of time.

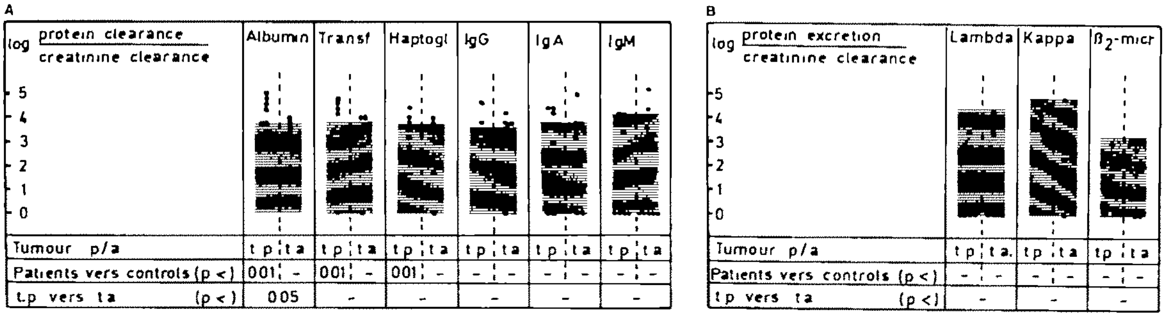
The non-parametric Mann-Whitney test was employed for statistical evaluations.

Results

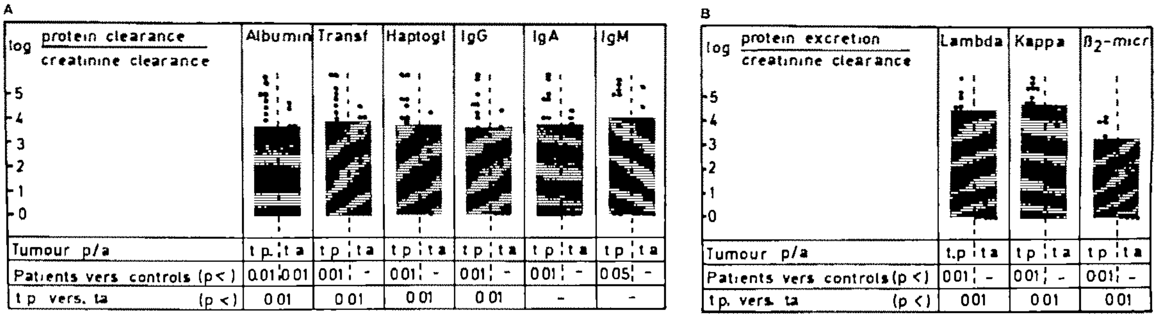
Figure 1 shows the protein excretion in 15 patients with grade I-II tumours, comparing patients with tumours present to those without tumours and to the control group.

Figure 2 demonstrates protein excretion in 16 patients with grade III-IV tumours, comparing patients with residual or recurrent tumours to those without tumours and to the control group. In addition, the clearances of haptoglobin, IgG and IgA were significantly increased in patients with grade III-IV tumours when compared to patients with grade I-II tumours ($P < 0.05$). The same held true for the excretion of the 3 low molecular weight proteins in patients with grade III-IV tumours when compared to patients with grade I-II tumours ($P < 0.01$).

Figure 3a illustrates the relative clearance of albumin, transferrin, and haptoglobin in a patient with an infiltrating grade II tumour treated by transurethral resection. Protein clearance never returned to normal and every cystoscopy demonstrated tumours. Following cystoscopy with repeated transurethral resections, the protein clearance decreased temporarily, except at 16 months after primary treatment. At that time a renal pelvis tumour was shown on an excretory urogram and 4 months later a nephroureterectomy was performed, revealing a grade II transitional cell tumour.



Figs. 1a and b Relative clearance of 6 high molecular weight proteins and relative excretion of 3 low molecular weight proteins in 15 patients with grade I-II transitional cell carcinoma of the urinary bladder, examined at cystoscopy 3 months after primary treatment. In 7 of the patients tumour was present (t.p.), and in the other 8 patients tumour was absent (t a). The grey coloured areas indicate the observed range of relative protein clearance in the control group.



Figs. 2a and b Relative clearance of 6 high molecular weight proteins and relative excretion of 3 low molecular weight proteins in 16 patients with grade III-IV transitional cell carcinoma of the urinary bladder, examined at cystoscopy 3 months after primary treatment. In 8 of the patients tumour was present (t.p.), and in the other 8 patients tumour was absent (t a). The grey coloured areas indicate the observed range of relative protein clearance in the control group.

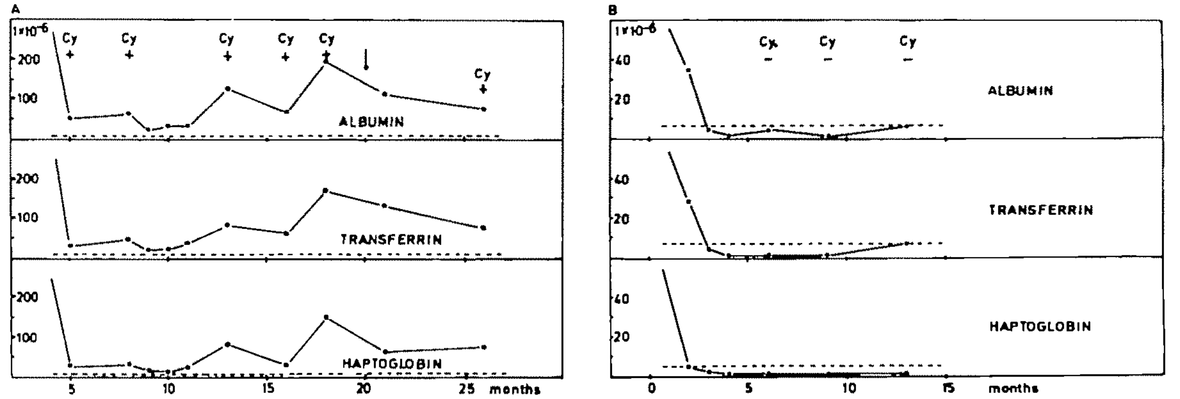
Figure 3b shows the relative protein clearance following successful radiotherapy of a patient with an infiltrating grade III tumour. Initially, the relative protein clearance was increased, but it decreased rapidly to normal after therapy. At the following cystoscopies no tumours were observed and the relative protein clearance remained normal.

Figure 3c demonstrates the same course as in Figure 3b in a patient treated successfully with radiotherapy and 6 months later with urinary diversion because of a severe radiation cystitis.

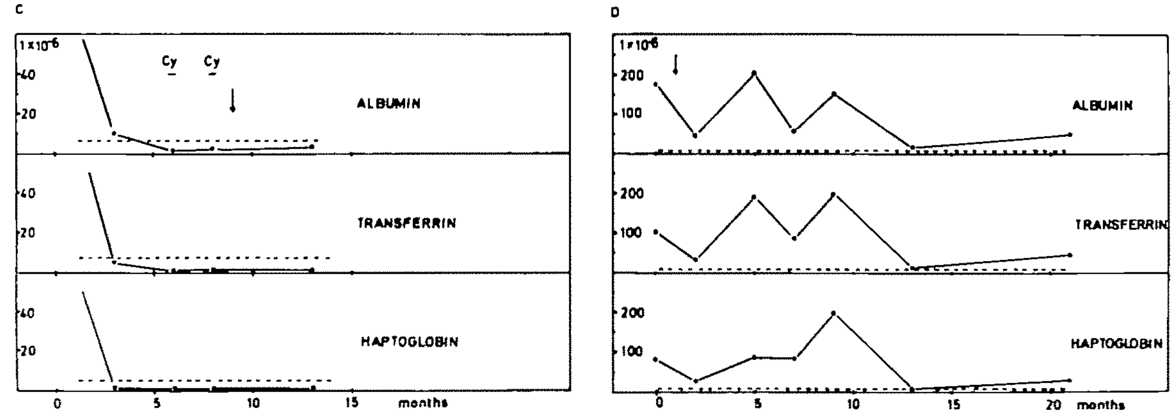
Figure 3d illustrates the relative protein clearance in a patient treated by cystectomy and urinary diversion because of an infiltrating squamous cell carcinoma. Post-operatively, the relative protein clearance remained increased and 3 months after primary treatment a large local residual tumour was demonstrated. This tumour was successfully controlled by radiotherapy and cytostatic drugs, followed by decreasing clearances.

Using the simultaneously increased relative clearance of albumin, transferrin, and haptoglobin as a diagnostic test to indicate residual or recurrent bladder tumours, the predictive value of this test was examined. Table 1 shows that in 17 out of 32 instances with grade I-II tumours present, increased relative protein clearance was demonstrated, and in 17 out of 24 instances with increased relative protein clearance a bladder tumour was present.

Table 2 shows that in all instances with grade III-IV tumours present, increased relative protein clearance was demonstrated and that the relative protein clearance was normal in 16 out of 18 instances without tumours. In 22 out of 24 instances with increased relative protein clearance a bladder tumour was present, corresponding to a predictive value of a positive diagnostic test of 92%. Normal relative protein clearance was always indicative of the absence of tumours, corresponding to a predictive value of a negative diagnostic test of 100%.



Figs. 3a and b Relative protein clearance in a patient with an infiltrating grade II transitional cell carcinoma of the urinary bladder Cystoscopy is indicated by Cy and presence of tumour by +. The arrow indicates nephroureterectomy. **3b** Relative protein clearance in a patient with an infiltrating grade III transitional cell carcinoma of the urinary bladder. Cystoscopy is indicated by Cy and absence of tumour by —. The horizontal dash-and-dotted lines indicate the upper range of relative protein clearance in the control group.



Figs. 3c and d Relative protein clearance in a patient with an infiltrating grade III transitional cell carcinoma of the urinary bladder Cystoscopy is indicated by Cy and absence of tumour by —. The arrow indicates urinary diversion. **3d** Relative protein clearance in a patient with an infiltrating squamous cell carcinoma of the urinary bladder The arrow indicates cystectomy and urinary diversion. The horizontal dash-and-dotted lines indicate the upper range of relative protein clearance in the control group.

Discussion

The increased urinary excretion of plasma proteins demonstrated in patients with urothelial bladder tumours may be caused by the admixture of proteins to urine from the tumour surface or by a glomerular lesion due to deposition of tumour derived antigen-antibody complexes.

Admixture of proteins, especially immunoglobulins, to urine from the tumour surface has been suggested in previous studies (Johansson *et al.*, 1971; Johansson and Ljungquist, 1974; Johansson and Kistner, 1975), since a significant relationship between the clinical tumour T-staging and the urinary protein excretion could be demonstrated. Both in the study of Johansson (1975) and in the present study, urinary protein excretion decreased after successful treatment or urinary diversion, but protein excretion did not return to normal. In these cases protein admixture from the tumour surface could not be responsible for the increased urinary protein excretion.

The immune response of bladder cancer patients to malignant bladder tumour cells has been reported by several investigators (Bubenik *et al.*, 1970; Herr, 1976; Catalona, 1977; Vilien and Wolf, 1978), and glomerular deposition of tumour derived antigen-antibody complexes has been demonstrated in connection with urothelial carcinoma (Jones *et al.*, 1975) as well as with other malignant diseases (Lewis *et al.*, 1971; Costanza *et al.*, 1973; Higgins *et al.*, 1974). These glomerular lesions may cause a nephrotic syndrome as in the latter studies or less pronounced protein excretion (Jones *et al.*, 1975; Ozawa *et al.*, 1975; Pascal *et al.*, 1976). The increased protein excretion demonstrated in the present study may be caused by such glomerular lesions, since a glomerular type of proteinuria was predominant (Figs. 1 and 2). This would also be in agreement with the persistence of increased protein excretion in patients with tumours, independent of urinary diversion. The heavier glomerular proteinuria with increased

Table 1 Diagnostic Value of Relative Protein Clearance in 15 Patients With Grade I-II Transitional Cell Carcinoma of the Urinary Bladder, Examined Simultaneously by Cystoscopy and Urinary Protein Profile in 63 Instances

Relative protein clearance	*Residual tumour*	*No tumour*	*Total*
Increased	17	7	24
Normal	15	24	39
Total	32	31	63

Table 2 Diagnostic Value of Relative Protein Clearance in 12 Patients With Grade III-IV Transitional Cell Carcinoma of the Urinary Bladder, Examined Simultaneously by Cystoscopy and Urinary Protein Profile in 40 Instances

Relative protein clearance	*Residual tumour*	*No tumour*	*Total*
Increased	22	2	24
Normal	0	16	16
Total	22	18	40

excretion of haptoglobin, IgG and IgA in patients with grade III-IV tumours indicates a more severe glomerular lesion than in patients with grade I-II tumours. The persistence of glomerular proteinuria in some tumour-free patients (Figs. 1 and 2) may be caused by persistent glomerular lesions, since protein admixture from the tumour surface could not be responsible for the increased excretion of high molecular weight proteins in these patients.

Using the increased relative clearance of albumin, transferrin and haptoglobin as a diagnostic test for the prediction of residual or recurrent tumours, the test appeared to be of limited value in patients with grade I-II tumours (Table 1). On the other hand, all patients with grade III-IV tumours showed an increased relative protein clearance, and the predictive value of a positive or negative test was 92% and 100% respectively (Table 2). This may be of clinical significance but evaluation of a larger group of patients is necessary.

Increased excretion of low molecular weight proteins was observed only in patients with residual or recurrent grade III-IV tumours (Fig. 2b). This finding is in accordance with earlier investigations of urinary protein excretion in patients with advanced neoplasms other than urothelial tumours (Rudman *et al.*, 1969; Bell and Chaplin, 1970; Hemmingsen and Skaarup, 1977b). In advanced malignancies several investigations have shown increased serum concentrations of immunoglobulin free light chains (Isobe and Ossermann, 1971; Solomon, 1976) and β_2-microglobulin (Evrin and Wibell, 1973; Schuster *et al.*, 1976). These proteins easily traverse the glomerular filter and are reabsorbed in the proximal tubules (Hardwicke, 1975). When filtered in excess due to high serum concentrations, the reabsorptive capacity of the proximal tubules may be exceeded, resulting in an increased urinary excretion. The increased excretion of the 3 low molecular weight proteins in our patients is probably caused by this overflow mechanism. However, impaired tubular reabsorption cannot be excluded.

A possible increase in bladder permeability for low molecular weight proteins due to radiotherapy should also be emphasised, since patients with grade III-IV tumours showed a heavier excretion of these proteins than was observed in patients with grade I-II tumours.

In conclusion, our results show that the relative clearance of high molecular weight proteins is increased both in patients with grade I-II and to a greater extent in patients with grade III-IV carcinoma of the urinary bladder. The increased relative clearance of albumin, transferrin and haptoglobin is of predictive value in the diagnosis of residual and recurrent grade III-IV tumours. The relative excretion of low molecular weight proteins is increased in patients with advanced tumours.

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Pre-operative Bladder Irrigation with Povidone-iodine

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Summary—The effectiveness of pre-operative disinfection of the bladder by irrigation with povidone-iodine was assessed in 40 patients with indwelling catheters who underwent transvesical prostatectomy.

The results were encouraging: in 75% of the cases sterilisation of the urine was achieved and in 12.5% counts were $< 10^5$ organisms/ml.

The management of the male patient with an indwelling urethral catheter is a problem in urology. The clinical course after prostatic surgery is associated with a high risk of infection. Islam and Chapman (1977) reported the incidence of post-operative infection to be 19.1%, while Bastable *et al.* (1977) found it to be 30%. Because of this high incidence of infection, administration of antibiotics is routine in some centres (Collste and Tornqvist, 1978). Others use bladder disinfection by continuous irrigation and closed-system drainage (Bourque, 1957; Roberts, 1965; Webb and Blandy, 1968; Symes *et al.*, 1972; Bastable *et al.*, 1977).

We have studied the use of polyvinyl-pyrrolidone iodine complex (povidone-iodine) in pre-operative bladder irrigation as a method of controlling post-operative infection.

Materials and Methods

Fifty patients with indwelling catheters and urinary tract infection were chosen for this trial and all had a transvesical prostatectomy. Three patients also had a concomitant hernioplasty and another 2 had a diverticulectomy. Prophylactic antibiotics were not administered either before or after operation.

The solution for irrigation was prepared by diluting commercial polyvinyl-pyrrolidone iodine complex 10% (povidone-iodine: Betadine (Napp Laboratories Ltd.)) with saline 1:4. On the eve of the operation the bladder was irrigated manually a few times with this solution in quantities of 100 ml. The solution was kept in the bladder for a total of 5 to 10 min and then emptied. The bladder was irrigated for a second time next morning.

The operative field was prepared by povidone-iodine (scrub and solution). During the operation urine was withdrawn from the closed bladder for culture. A piece of bladder mucosa from the margin of the opened bladder (approximately 5×10 mm) and a piece of prostatic urethra were also sent for culture.

The patients received general post-operative care but antibiotics were withheld. Povidone-iodine was not used post-operatively.

Forty patients were thus prepared for operation. Another 10 patients served as controls, their bladders being irrigated with saline only. Urine was examined for infection post-operatively, as well as any discharge from the operative wounds.

Urine samples of 0.01 ml were seeded on to plates of MacConkey medium with a 4 mm needle. The colonies were counted after incubation for 24 h at 37°C. The remaining urine was centrifuged for 5 min; then a slide was prepared from the sediment and stained by Gram's method.

A sample from the colonies was inoculated on 3 culture media—Kligler (Table 1), Citrate and Mio (Table 2), for determination of the species.

The tissue samples were incubated in thioglycolate broth in a Gas-Pak anaerobic system for 24 h, as well as on blood-agar, MacConkey and BHI-agar.

Results

Two patients had some irritation and painful contraction of the bladder during the irrigation, but generally it was well tolerated. One patient had severe pain and refused to have the second morning session irrigation.

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Table 1

	Kligler Iron Agar (Difco Laboratories, USA)
	For biochemical tests
Beef extract	3 g
Yeast extract	3 g
Peptone	15 g
Proteose peptone	5 g
Lactose	10 g
Dextrose	1 g
Ferrous sulphate	0.2 g
Sodium chloride	5 g
Sodium thiosulphate	0.3 g
Agar	12 g
Bacto phenol red	0.024 g per litre

The results of the pre-operative and intra-operative cultures are summarised in Figure 1. There were 18 isolates of *Escherichia coli*, 7 of *Proteus* spp., 4 of *Pseudomonas* spp., 5 of *Klebsiella* spp., 5 of *Enterobacter* spp. and 1 *Staphylococcus albus* isolated from cultures taken pre-operatively.

In the povidone-iodine treated group, only 5 patients remained infected (Fig. 2). *Esch. coli* was isolated from the urine and from the wound of one patient, *Proteus mirabilis* in another, and *Pseudomonas aeruginosa* in a third. One patient, who had infection with *Proteus* spp. pre-operatively, developed a wound infection with *Proteus* spp. One of the patients with *Enterobacter* infection continued to secrete this organism post-operatively in his urine. In 4 cases bladder mucosa cultures yielded less than 100,000 colonies: one case each of *Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella* spp. and *Esch. coli.* The urine in these patients was sterile.

In the control group all but one of the patients were febrile for at least 2 to 3 days, until antibiotics were administered. Urine was infected and so were some of the wounds.

The post-operative stay in hospital was from 8 to 14 days (average 11.1).

There were no deaths in the series. No untoward reactions against povidone-iodine were noted except for one patient with severe pain (see above).

Table 2

	Mio substract
Decarboxylase medium	9.0 g
Peptone	5.0 g
Triptone	10.0 g
Agar	2.0 g
L-Orbenine	5.0 g per litre at pH 6.5

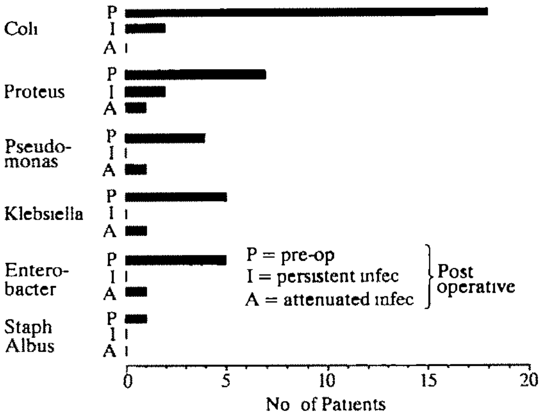

Fig. 1
Pre-operative and intra-operative cultures.
P = Pre-operative urine culture.
I = Persistent infection
A = Light infection (less than 100,000 colonies per ml).

Discussion

The infection rate after prostatectomy varies widely from 19.1% (Islam and Chapman, 1977) to 30% (Bastable *et al.*, 1977). About 50% of the catheterised patients were infected after 10 to 13 days (Akiyama and Okamoto, 1979), and in those who underwent prostatectomy after a long period of indwelling catheterisation the proportion was even higher.

Much has been written on the prevention of post-operative infection, be it by prophylactic

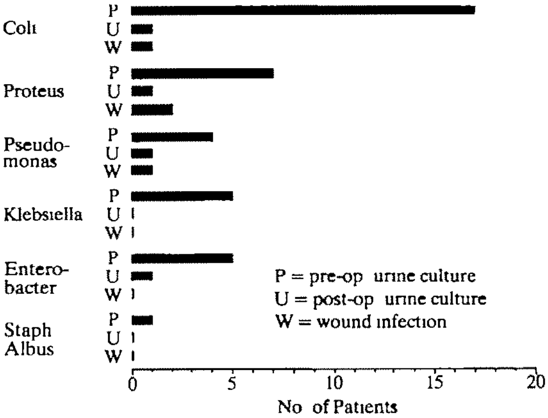

Fig. 2
Pre-operative and post-operative cultures.
P = Pre-operative urine culture.
U = Post-operative urine culture.
W = Post-operative wound infection.

bladder irrigation with various solutions (Bourque, 1957; Bastable *et al.*, 1977). Routine systemic antibiotic prophylaxis is clearly not the answer, and is likely to do more harm than good (*Lancet*, 1976).

Povidone-iodine has been widely used as an antimicrobial prophylaxis or treatment in wound infections, burns, peritonitis, vaginal infections, *etc.*, as well as for bladder irrigation pre-operatively and post-operatively in sterile cases (Hubmann, 1977).

Povidone-iodine is a complex of polyvinyl pyrrolidone and iodine, water soluble and of high molecular weight, that is non-toxic and non-sensitising to human tissue. The available iodine is released at a very slow rate from the complex, prolonging the germicidal action of the free iodine. The germicidal action of povidone-iodine has been demonstrated up to at least 4 h after a single application (Connell and Rousselot, 1964). It has also been proved safe for patients hypersensitive to inorganic iodine and no evidence of development of bacterial resistance has been demonstrated (*Lancet*, 1976).

In a preliminary trial we used a solution of povidone-iodine diluted with saline 1:1, but had to increase the dilution successively to 1:2, 1:3 and 1:4 because of painful irritation of the bladder. The concentration of 2% is tolerated quite well, and that is the solution we used in the present work. Hubmann (1977) used the 10% povidone-iodine solution diluted 1:10.

Povidone-iodine bladder irrigation solution eradicated infection in 75% of the infected bladders in our series, reduced the severity of the infection (cultures less than 100,000 per ml) in 12.5% and failed in 12.5%. These reduced but positive cultures were obtained only from the bladder mucosa and not from the urine. These results are encouraging.

Povidone-iodine is recommended at least in all cases of pre-operative bladder infection as a result of indwelling catheters.

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Fourth Report on the Standardisation of Terminology of Lower Urinary Tract Function

Terminology related to neuromuscular dysfunction of the lower urinary tract

PRODUCED BY THE INTERNATIONAL CONTINENCE SOCIETY*

Members: C. P. Bates, W. E. Bradley, E. S. Glen, H. Melchior, D. Rowan, A. M. Sterling, T. Sundin, D. Thomas, M. Torrens, R. Turner-Warwick, N. R. Zinner and T. Hald (Chairman)

This report deals with recommendations on terminology related to neuromuscular dysfunction of the lower urinary tract with particular reference to classification of the neuropathic bladder.

These standards are proposed to facilitate comparison of results by investigators who use urodynamic methods. It is recommended that the acknowledgement of these standards in written publications be indicated by a footnote to the section "Methods and Material" or its equivalent: "Methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted".

Lower Urinary Tract Dysfunction

This may be caused by:

(1) Disturbance of the pertinent nervous or psychological control systems.
(2) Disorders of muscle function.
(3) Structural abnormalities.

The term *neuromuscular dysfunction* includes the first 2 categories.

Classifications based on concepts of the cause of a dysfunction, especially on the site of a neurological lesion, may be confusing. A lesion is often difficult to locate with certainty and different lesions may produce identical functional changes in the lower urinary tract.

Therefore such a classification gives little help when considering the management of the end organ abnormality. Without objective information about the function it is impossible to compare results of treatment from different centres. An underlying neurological pathology is, of course, equally important from a prognostic, therapeutic and counselling point of view and must be considered at the same time.

The increasing use of urodynamic methods has made it possible to classify disorders of the detrusor and urethral closure mechanism with some accuracy. However, the range of bladder and urethral abnormalities cannot fully be defined at the present time.

This report presents a basic classification of function. Only neuromuscular function is considered, leaving structural organ changes and complicating factors aside. The lower urinary tract is composed of the *bladder* and *urethra*. They form a functional unit and their interaction cannot be ignored. Each has 2 functions: the bladder to store and void, the urethra to control and convey. When a reference is made to the hydrodynamic function or to the whole anatomical unit as a storage organ—the vesica urinaria—the correct term is the *bladder*. When the specific smooth muscle structure known as the m. detrusor urinae is being discussed, the correct term is the *detrusor*.

For simplicity the bladder/detrusor and the urethra will be considered separately so that a classification based on a combination of functional anomalies can be reached. No attempt has been made to define these in a quantitative way or to consider efficiency. *Sensation* cannot be accurately evaluated, but must be assessed. This classification depends on the results of various objective urodynamic investigations. The number of specific tests may vary from one person to another. Studies of the filling and voiding phases are essential for each patient.

Terms used should be objective, definable and ideally should be applicable to the whole range of abnormality. When authors disagree with the classification presented below, or use terms that have not been defined here, their meaning should be made clear.

---

* Produced following discussion at the International Continence Society Meetings in Manchester, September 1978 and in Rome, October 1979.

Detrusor Function

The detrusor function may be:

1. normal
2. overactive
3. underactive

Activity in this context is related to detrusor contractions interpreted from intravesical (p_{ves}) or detrusor pressure (p_{det}) changes, preferably the latter. Assessment of activity must be made during both filling and voiding, and the classification may change between these 2 phases.

Normal Detrusor Function

During the filling phase the bladder contents increase in volume without a significant rise in pressure (accommodation). No involuntary contractions occur despite provocation. Normal voiding is achieved by a voluntarily initiated detrusor contraction that is sustained and can be suppressed voluntarily. A normal detrusor so defined may be described as "stable".

Overactive Detrusor Function

Overactive detrusor function is indicated when during the filling phase there are involuntary detrusor contractions, which may be spontaneous or provoked, that the person cannot suppress. Provocation includes rapid filling, alterations of posture, coughing, walking, jumping and other triggering procedures. Voiding may be due to involuntary contractions or to voluntary contractions that cannot be suppressed. Various terms have been used to describe these features and they are defined as follows:

The *unstable detrusor* is one that is shown objectively to contract, spontaneously or on provocation, during the filling phase while the patient is attempting to inhibit micturition. The unstable detrusor may be asymptomatic and its presence does not necessarily imply a neurological disorder.

Detrusor hyperreflexia is defined as overactivity due to disturbance of the nervous control mechanisms. Whether the unstable detrusor is synonymous with detrusor hyperreflexia is unknown at present. Until this controversy is resolved, detrusor hyperreflexia should be confirmed by objective evidence of a neurological disorder.

The use of conceptual and undefined terms such as hypertonic, systolic, uninhibited, spastic and automatic should be avoided. When referring to the volume/pressure relationship in a bladder with a high pressure rise the correct term is a *low-compliance bladder* (*e.g.* a shrunken bladder following radiotherapy).

Underactive Detrusor Function

In the underactive detrusor there are no contractions during filling. During voiding the contraction may be absent or inadequately sustained. *A non-contractile detrusor* is one which does not contract under any circumstances. *Detrusor areflexia* exists where underactivity is due to an abnormality of nervous control and denotes the complete absence of centrally coordinated contraction. In detrusor areflexia due to a lesion of the conus medullaris or sacral nerve outflow, the detrusor should be described as *decentralised*—not denervated, since the peripheral neurones remain. The bladder function may be described as *autonomous*. In such bladders pressure fluctuations of low amplitude may occur. The use of terms such as atonic, hypotonic, autonomic and flaccid should be avoided. If the volume/pressure relationship of a bladder is referred to as being capacious with little change in pressure, then the correct term is a *high-compliance bladder*.

Urethral Function

The urethral closure mechanism may be:

1. normal
2. overactive
3. incompetent

Normal Urethral Closure Mechanism

The *normal* urethral closure mechanism maintains a positive urethral closure pressure during filling even in the presence of increased abdominal pressure. It may be overcome by detrusor overactivity. During micturition the normal closure pressure decreases to allow flow. The normal closure mechanism is capable of interrupting urination voluntarily.

Overactive Urethral Closure Mechanism

An *overactive* urethral closure mechanism contracts involuntarily against a detrusor contraction or fails to relax at attempted micturition.

Synchronous detrusor and urethral contraction is *detrusor/urethral dyssynergia*. This diagnosis should be qualified by stating the location and type of the urethral muscles (striated or smooth) which are involved (Fig.).

Despite the confusion surrounding "sphincter" terminology the use of certain terms is so widespread that they are retained and defined here. The term *detrusor/sphincter dyssynergia* describes a detrusor contraction concurrent with an inappropriate contraction of the urethral and/or periurethral striated muscle. In the absence of other neurological features the validity of this diagnosis should be questioned. The term *detrusor/bladder neck dyssynergia* is used to denote a detrusor contraction concurrent with an objectively demonstrated defect of bladder neck opening. No parallel term has been elaborated for possible detrusor/distal urethral (smooth muscle) dyssynergia.

Incompetent Urethral Closure Mechanism

An *incompetent* urethral closure mechanism allows leakage of urine. The negative urethral closure pressure may be persistent (continuous leakage) or due to a rise in abdominal pressure (genuine stress incontinence) or an involuntary fall in intraurethral pressure in the absence of detrusor activity (unstable urethra). Detrusor overactivity is more likely to be accompanied by leakage if there is an involuntary decrease in urethral pressure.

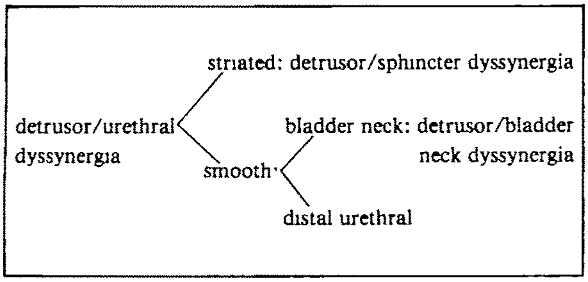
striated: detrusor/sphincter dyssynergia
detrusor/urethral dyssynergia
bladder neck: detrusor/bladder neck dyssynergia
smooth
distal urethral

Fig.

Sensation

Sensation is difficult to evaluate because of its subjective nature. It is usually assessed by questioning the patient in relation to the fullness of the bladder either during the taking of the clinical history or during cystometry. There are 2 groups of sensory modalities: proprioception, which serves to inform on tension and contraction, and exteroception, which serves to inform on pain, touch and temperature. Sensation can be classified broadly as follows:

1. normal
2. hypersensitive
3. hyposensitive.

Previous Reports on the Standardisation of Terminology of Lower Urinary Tract Function

First Report:

British Journal of Urology (1976), **48**, 39-42.
European Urology (1976), **2**, 274-276.
Urologia Internationalis (1976), **32**, 81-87.
Scandinavian Journal of Urology and Nephrology (1977), **11**, 193-196.
Urologe A (1976), **15**, 93-96.
Journal d'Urologie et de Néphrologie (Paris) (1976), **6**, 429-436

Second Report:

British Journal of Urology (1977), **49**, 207-210.
European Urology (1977), **3**, 168-170.
Scandinavian Journal of Urology and Nephrology (1977), **11**, 197-199
Urologe A (1980), **19**, 189-191

Third Report:

British Journal of Urology (1980), **52**, 348-350.
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Urologe A (1980), **19**, 315-317.

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A Study of Cefamandole Prostatic Tissue Levels

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Summary—Cefamandole is a new cephalosporin with a broad spectrum activity. A study was undertaken to determine the distribution of cefamandole in the prostate gland. It was found that the drug was concentrated in the prostate gland and that the concentration was dose related.

Cefamandole is a new cephalosporin derivative with a broad spectrum activity, particularly against *Esch. coli, Staph. aureus, Staph. epidermis, Enterobacter* species, *Salmonella* species, *Haemophilus influenzae* and many hospital acquired infections due to cephalothin-resistant micro-organisms (Neu, 1974). Studies indicate that cefamandole diffuses readily from the serum into soft tissue interstitial fluid. The concentration of the antibiotic in bile and urine is greater than necessary to kill susceptible pathogenic bacteria present in these fluids (Waterman *et al.*, 1976). Correlation of *in vitro* studies with pharmacokinetic properties revealed that cefamandole would inhibit most susceptible Gram-positive and Gram-negative bacteria (Griffith *et al.*, 1976). The objective of the study was to establish whether the high peak serum levels produce significant prostatic tissue levels.

Patients and Methods

Thirty patients planned to have a prostatectomy were admitted into the study. All patients had a mid-stream urine sample taken, examined microscopically and cultured. The patients were divided into 3 groups of 10 patients, each receiving 2 g of cefamandole intravenously (iv), 1 g of cefamandole (iv) or 1 g of cefamandole intramuscularly (im) one hour before the operation with the premedication. As there is a high urine concentration of cefamandole following parenteral administration (Waterman *et al.*, 1976), bladder washout was done with distilled water following routine cystoscopy prior to prostatectomy to avoid the possibility of any increased antibiotic concentration in prostatic tissue being due to contamination from urine.

Transurethral resection of the prostate was performed in 15 patients and 15 had a retropubic prostatectomy. When the prostatic tissue was obtained, 10 ml of blood were taken simultaneously in a heparinised bottle. The blood was centrifuged and the plasma removed into a plain bottle. Both plasma and prostatic tissue were frozen to a temperature of −20°C within the next 20 min.

Prostatic tissue for analysis was removed from the central core of tissue after trimming the outside tissue away.

Assay Method

The assays were performed by a large plate agar diffusion technique by incorporating *B. subtilis* NCTC 10400 into 100 ml of Penassay seed agar (Difco) and pouring into 10 in. square glass assay dishes (Mast Laboratories). The samples were applied by impregnation into 6 mm diameter blotting paper discs (Mast Laboratories) and applied to the plate according to a random code pattern.

For the serum assays the standards were prepared in pooled normal human serum. The range of standard concentrations was 1.25 to 20 mg/l and any test samples having values >20 mg/l were diluted in normal serum to fall within the standard range.

For the tissue assays the samples were frozen at −20°C and then approximately 1 g of each tissue was finely chopped with a scalpel. The amount of tissue was checked by weighing and an equal amount of M/15 phosphate buffer pH 6.6 was added to each. The extractions were carried out for 2 h at 4°C with vigorous shaking every 10 min. At the end of 2 h the extracts were centrifuged

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and the supernatant fluid used to impregnate the assay discs. These were compared against standards prepared in M/15 phosphate buffer pH 6.6, the tissue extracts having half the concentration of antibiotic of the original tissue.

Following overnight incubation at 37°C the zones of inhibition were measured on a Leebrook zone reader and the test concentrations calculated.

Results

Serum levels of cefamandole varied from 12.2 μg/ml to 90.0 μg/ml in Group I (2g—iv), from 8.7 μg/ml to 50.3 μg/ml in Group II (1g—iv) and from 14.9 μg/ml to 36.0 μg/ml in Group III (1g—im). The corresponding prostatic tissue levels of the drug ranged from 11.0 μg/g to 37.5 μg/g in Group I (2g—iv), from 8.0 μg/g to 27.0 μg/g in Group II (1g—iv) and from 24.6 μg/g to 21.7 μg/g in Group III (1g—im). The paired results showed a possible relationship between serum and prostatic tissue levels of the drug (Fig.). The time interval between cefamandole administration and blood/tissue sample collection is shown in Table 1.

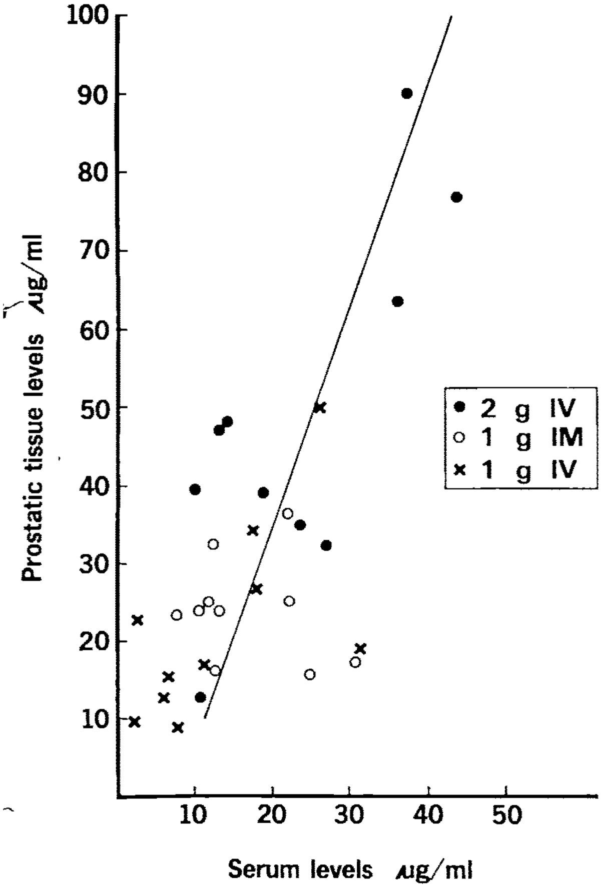

Fig.

Discussion

The concentration of most antibiotics in organs is usually determined by homogenising the whole tissue. This can be misleading since all tissue homogenates consist of a mixture of materials and blood contamination must be excluded. The value of antibiotic concentration in tissue homogenates can also be misleading when the site of infection in the tissue, *e.g.* prostate gland, is on the excretory side of the epithelial membrane. Most of the antimicrobial drugs cannot cross the prostatic epithelium into prostatic fluid. Stamey *et al.* (1970) suggested that the factors determining diffusion and concentration of an antibiotic into the prostatic fluid are: lipid solubility of the drug, degree of drug ionisation in plasma and the degree of protein binding of the drug. A lipid insoluble drug will be distributed largely into the extracellular fluid compartment since it cannot cross epithelial membranes. If a drug is lipid soluble, it is only the non-ionised fraction that can cross the epithelial membrane. The degree of ionisation in plasma (determined by the pKa of the drug) directly determines the non-ionised fraction available for diffusion. The antibiotic must have an optimal biological activity against the causative organisms at pH 6.6 (*i.e.* the normal pH of prostatic secretion). No antibiotic has been found to fulfil all of these requirements.

Cefamandole is a new cephalosporin which has a pKa of 4.9. The percentage of protein binding of cefamandole found in previous studies by Barza *et al.* (1976), Griffith *et al.* (1976), Fong *et al.* (1976) and Neu (1978) were 67, 70, 74 and 70%. It appears that 25 to 35% of cefamandole existed as the free compound. *In vitro* studies by Neu (1974) showed the susceptibility of selected

Table 1

Time in minutes	*50*	*60*	*90*	*110*
Group I (2g—iv)	1	5	—	4
Group II (1g—iv)	—	1	4	5
Group III (1g—im)	2	6	—	2

Time interval between cefamandole administration and blood/tissue sample collection.

Table 2 *In Vitro* Study of Susceptibility of Selected Organisms to Cefamandole

Organism	*No of isolates*	*Per cent susceptible at (μg/ml) of*							
		<0.8	*0.8*	*1.6*	*3.12*	*6 5*	*12 5*	*25*	*30*
Staph. aureus	56	71	93	100					
Str faecalis	25							100	
Esch coli.	60		27	70	80	87	88	93	95
Proteus mirabilis	43		9	86	90			96	100

(Susceptibility studies determined by a microtiter broth dilution technique with 10^4 inoculum) (Neu, 1974).

organisms to cefamandole as in Table 2. Bullen *et al.* (1979) studied the cefamandole levels in skeletal muscle and subcutaneous fat samples taken from patients during amputation of the lower limb for severe ischaemia. Bactericidal concentrations of the drug were achieved in both muscle and fat. The 3 different groups of patients in the present study showed a definite concentration of the drug in their sera and prostatic tissues. The drug concentrations were dose related.

These results seem to indicate that cefamandole, a new cephalosporin with a broad spectrum activity, diffuses rapidly from serum into prostatic tissue and that the concentration in the prostate is dose related. However, the blood/tissue concentrations reported represent single spot samples, *i.e.* only one value per study. As all blood/tissue concentration studies have a problem of relating time from dose to sample concentration, a serial study should be carried out in the future to determine the rate of distribution into and out of the prostate and also to compare this with the blood concentration curve. The comparison of prostatic tissue levels of the drug with prostatic fluid levels was beyond the scope of this study.

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I am grateful to Mr P. F Philip and Mr Grant Williams, Consultant Urologists at Charing Cross Hospital, for allowing me to include their patients in the study. I should also like to thank Dr D. S. Reeves, Consultant Microbiologist at Southmead Hospital, Bristol, for assessing the tissue and blood levels, and Dr K. Woodcock and Miss K. M. Legg from Eli Lilly & Company Limited for supplying the antibiotic.

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Short-term Antibiotic Prophylaxis and Prostatectomy*

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Summary—Two hundred patients undergoing prostatic surgery at 2 hospitals were randomly allocated into 4 equal groups. The groups were a control, cephalexin, co-trimoxazole and carfecillin treated groups. The incidence of urinary tract infections and other complications of prostatic surgery were studied in each group after a short-term prophylactic regime of 3 doses of the antibiotic. The incidence of urinary infection was significantly improved from 28% in the control group to 8% and 16% in the co-trimoxazole and cephalexin groups respectively. Carfecillin was not effective in reducing urinary infection. However, all 3 antibiotics reduced the incidence of other infective sequelae.

The incidence of urinary tract infection following prostatectomy varies widely in different urological centres. Rates of infection of between 6 and 62.5% have been reported (Lacy *et al.*, 1971; Symes *et al.*, 1972). Various techniques aimed at reducing this incidence have been tried with differing degrees of success. A careful aseptic technique during catheterisation, closed catheter drainage, "no catheter" technique, auto-irrigation with diuretics in the post-operative period, irrigation with antimicrobial solutions and prophylactic antibiotics have all been shown to reduce the incidence of urinary infection (Cass, 1969; Essenhigh and Eustace, 1970; Symes *et al.*, 1972; Morris *et al.*, 1976; Bastable *et al.*, 1977).

Chodak and Plaut (1979) reviewed 75 papers devoted to the subject of antibiotic prophylaxis and prostatectomy. They found that many studies were retrospective, uncontrolled and contained only small numbers of patients. They also found little support for the use of prophylactic antibiotics.

This report of the use of short-term antibiotic prophylaxis and prostatectomy investigates the incidence of urinary tract infection at 2 centres in a prospective study of 200 patients randomly allocated into a control and 3 antibiotic-treated groups.

Patients and Methods

All patients with urinary outflow obstruction undergoing prostatectomy were considered for inclusion in the study. Patients were excluded if they were found to have pre-operative urinary infection or were on current antibiotic therapy. Urethral catheterisation was performed for the relief of painful retention of urine or intractable urinary symptoms in patients with chronic retention of urine with overflow. An aseptic technique was used. The glans penis was cleaned with aqueous chlorhexidine gluconate 0.015% $^{w}/_{v}$ and cetrimide 0.15% $^{w}/_{v}$. The urethra was anaesthetised with 2% lignocaine hydrochloride and chlorhexidine 0.05% gel. The catheter was connected to a drainage bag (Sterilin). The study patients were randomly allocated to one of 4 groups:

1. Control.
2. Cephalexin 500 mg (Glaxo Laboratories).
3. Trimethoprim 160 mg/sulphamethoxazole 800 mg (Wellcome).
4. Carfecillin 500 mg (Beecham Laboratories).

Each antibiotic was given orally:

(*a*) 6 h pre-operatively;
(*b*) 6 h post-operatively;
(*c*) 12 h post-operatively.

Panendoscopy was performed prior to prostatic surgery. Transurethral resection of the prostate or retropubic prostatectomy was then performed. Following surgery, patients were catheterised with a 22 FG 3-way Foley catheter and irrigation with normal saline commenced. Irrigation was continued until the urine became clear, usually within 24 h.

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Table 1 Modes of Clinical Presentation of Patients with Urinary Outflow Obstruction

No. of cases	*Control*	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
	50	*50*	*50*	*50*
Presentation				
a. Prostatism	28	30	26	29
b. Acute retention	14	14	13	9
c Chronic retention	4	2	6	4
d. Acute on chronic retention	4	4	5	8

Urine specimens were obtained for culture on alternate days post-operatively until discharge and finally at 6 weeks in the follow-up clinic. Urine was cultured using the Sleigh filter paper dipstick method for semiquantitative analysis and on Cled culture medium. Sensitivities were tested on a circular Stokes plate using Mastering discs. The diagnosis of urinary tract infection rested upon a positive organism culture of $>100\times10^6$/1. The presence of white cells alone did not lead to a diagnosis of urinary infection. Organism cultures of $<100\times10^6$/1 were not accepted as a diagnosis of urinary infection and the culture was therefore repeated.

Septicaemia was diagnosed when a pyrexia of 38.5°C and rigors occurred in the post-operative period. In these cases urine and blood cultures were obtained and antibiotic therapy commenced empirically. Daily examination of the patient, including auscultation of the chest, was performed. Where abnormal signs were encountered a chest X-ray was obtained along with sputum for culture. Swabs from the Pfannenstiel wound were taken when evidence of infection was present, *i.e.* redness, swelling or purulent discharge.

Results

Two hundred patients were distributed into 4 groups of 50 patients. The majority of patients in each group presented with symptoms of urinary outflow obstruction (Table 1); however, a proportion in each group had developed acute or chronic retention. The incidence of each presentation in each study group was similar. The histology of the prostate was recorded in each case and the ratio of benign to malignant prostates was similar in each group (Table 2). The incidence of urinary tract infection in the control group was 28% (Table 3). Antibiotic prophylaxis with carfecillin failed to reduce the incidence of urinary tract infection. However, both co-trimoxazole and cephalexin reduced the incidence of infection to 8% and 16% respectively. Statistical analysis showed there to be statistical significance between the groups treated with co-trimoxazole and cephalexin and the control group ($P>0.01$, $P>0.02$ respectively).

The incidence of urinary tract infection varied according to the mode of presentation (Table 4). In each group the incidence of infection was less where catheterisation had not been necessary prior to surgery. Patients with chronic retention who

Table 2 Histology of the Prostate Removed

	Control	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
Benign	38	38	43	40
Malignant	12	12	7	10
Total	50	50	50	50

Table 3 Incidence of Infective Sequelae of Prostatic Surgery

	Control	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
No. of cases in study group	50	50	50	50
Urinary infections	14	8	4	16
Septicaemias	2	1	1	1
Respiratory infections	6	2	1	1

Table 4 Incidence of Urinary Infection

	Control	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
Prostatism	$^{7}/28$	$^{5}/30$	$^{1}/26$	$^{8}/29$
Acute retention	$^{6}/14$	$^{3}/14$	$^{3}/13$	$^{2}/9$
Chronic retention				
No catheter	$^{1}/4$	$^{0}/2$	$^{0}/6$	$^{0}/4$
With catheter	$^{1}/4$	$^{0}/4$	$^{0}/5$	$^{5}/8$

had not required catheterisation did not develop urinary tract infections in the antibiotic-treated groups. The figures, however, are too small to allow any statistical analysis of their significance. Both the retropubic and transurethral operations were associated with a similar incidence of infection when compared in each group. Malignant prostates tended to be associated with a smaller incidence of urinary infection in the antibiotic-treated groups (Table 5), except in those patients treated with co-trimoxazole.

Five patients developed clinical evidence of septicaemia with high pyrexia > 38.5°C and rigors. However, no organisms were cultured from blood cultures taken during the septicaemic episodes. Each patient recovered satisfactorily when treated with empirical antibiotics.

In both the co-trimoxazole and cephalexin-treated groups the majority of organisms cultured from urine specimens were resistant to the trial antibiotic (Table 6). However, the majority of the organisms cultured from urinary infections in the carfecillin-treated group of patients were sensitive to the penicillin antibiotics (Table 6).

Discussion

Many factors are responsible for the development of urinary tract infection after prostatectomy. Organisms may be introduced at the time of catheterisation, at surgery or at any time in the post-operative period. A careful aseptic technique is mandatory whenever the urinary tract is being manipulated. This is particularly important in the post-operative period, when the closed drainage system may have to be broken to wash out clots or to change the drainage bag. Prolonged surgical procedures may also predispose to the development of infection.

The infection rate in the control group was 28%. This figure is consistent with figures quoted from other centres. Jackaman and Chisholm (1975) reported an incidence of 31%, Bastable *et al.* (1977) 30% and Morris *et al.* (1976) 26% in their

Table 5 Incidence of Urinary Infection According to Prostatic Histology

	Control	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
Benign	$^{10}/38$	$^{7}/38$	$^{3}/43$	$^{15}/40$
Malignant	$^{5}/12$	$^{1}/12$	$^{1}/7$	$^{1}/10$

Table 6 Organisms Cultured from Urinary Tract Infections and Sensitivity to Prophylactic Antibiotics

Organism	*Cephalexin*			*Co-trimoxazole*			*Carfecillin*		
	No.	*Sensitive*	*Resistant*	*No.*	*Sensitive*	*Resistant*	*No.*	*Sensitive*	*Resistant*
Esch. coli	5	3	2	2	1	1	10	7	3
Enterococci	2	0	2	0	0	0	1	1	0
Staph. aureus	0	0	0	0	0	0	1	0	1
Str. faecalis	0	0	0	1	0	1	1	1	0
Proteus	0	0	0	0	0	0	1	1	0
Pseudomonas	0	0	0	0	0	0	0	0	0
Acinetobacter	1	0	1	1	0	1	2	0	2
Total organisms cultured	8	3 (37.5%)	5 (62.5%)	4	1 (25%)	3 (75%)	16	10 (62.5%)	6 (37.5%)

reviews of urinary tract infection after prostatectomy. The duration of catheterisation is probably the most significant influence on infection rates (Jackaman and Chisholm, 1975). Patients in our series who developed urinary infection in each study group had required indwelling catheters for a longer period both pre-operatively and post-operatively than those free from infection (Table 7).

The use of post-operative irrigation with antiseptic solutions has been shown to affect the incidence of urinary infection. Bastable *et al.* (1977) showed that when using saline irrigation in the post-operative period an incidence of 50% urinary infection was obtained; this was reduced to 31% when chlorhexidene irrigation was used. In our series, however, an infection rate of 28% in the control group occurred with routine irrigation with saline in the post-operative period.

Symes *et al.* (1972) described an infection rate of 5% after prostatectomy when a closed catheter drainage system combined with antiseptic solutions in the drainage bag was used. All of the patients studied in their series did not require indwelling catheters prior to surgery; all had presented with prostatism. Preservation of the closed drainage system is ideal but is not always possible, since interruption of the closed system may be necessary in order to evacuate clots or to change a drainage bag. Any interruption in the closed drainage system will allow organisms to gain access to the lower urinary tract.

Chodak and Plaut (1979) reviewed 75 papers on the subject of antibiotic prophylaxis in urological surgery in the English literature in the last 28 years. They found that few studies were of real value. Many were uncontrolled, retrospective or contained only small numbers of patients.

Morris *et al.* (1976) used a combination of kanamycin and co-trimoxazole and successfully reduced the rate of urinary infection from 26 to 5%. However, their patients received a 3-week course of co-trimoxazole. In our study, a regime of 3 doses of prophylactic co-trimoxazole reduced the infection rate from 28 to 8%, a highly significant result when one considers the short duration of treatment.

Marshall (1967) found no significant improvement in the infection rate after prostatectomy when penicillin and Sulphatriad were used in combination, whereas Korbel and Maher (1976) found amoxycillin produced a significant reduction in infection rates after transurethral surgery from 50% to 0%. However, their patients underwent either cystoscopy or resection of bladder tumours.

Although 62.5% of organisms cultured from the urine of carfecillin-treated patients were sensitive to the penicillin group of antibiotics, we were unable to show any reduction in the incidence of urinary infection with carfecillin prophylaxis. It is possible that a longer prophylactic course with this antibiotic would be more effective. Previous effective antibiotic prophylactic regimes in this group of patients involved durations of treatment of 7 days or longer (Genster and Madsen, 1970; Korbel *et al.*, 1976). Lacy *et al.* (1971), using cephaloridine prophylaxis, found an infection rate of 28% after prostatectomy, whereas in their control group the infection rate was 62.5%. Using short-term cephalexin our infection rate was 16%. The 3-dose regime in our study, therefore, was more effective than that of Lacy *et al.*, who used prophylaxis for a mean of 7.6 days.

A comparison of the incidence of urinary tract infection in each unit involved in this report revealed a greater overall incidence of infection in Hammersmith Hospital. This finding applied to each study group (Table 8). The organisms responsible for infection in each unit were similar,

Table 7 Mean Duration of Catheterisation in Days and its Relationship to Infection

	Control	*Cephalexin*	*Co-trimoxazole*	*Carfecillin*
Pre-operative catheter				
Infected	1.5	0.9	6.3	4.0
Non-infected	1.0	2.4	1.3	1.0
Post-operative catheter				
Infected	7.4	3.9	9.0	4.9
Non-infected	5.3	3.9	5.3	3.8
Overall duration				
Infected	8.9	4.7	15.3	8.9
Non-infected	6.4	7.4	6.6	4.1

Table 8 Incidence of Urinary Infection in Each Centre

		Norfolk and Norwich	*Hammersmith*
Control	50	$^{11}/_{43}$	$^{3}/_{7}$
Cephalexin	50	$^{4}/_{30}$	$^{4}/_{20}$
Co-trimoxazole	50	$^{1}/_{28}$	$^{3}/_{22}$
Carfecillin	50	$^{7}/_{28}$	$^{9}/_{22}$

but certain organisms were peculiar to each unit. *Pseudomonas*, enterococci and *Proteus* were encountered in Norwich, whereas *Str. faecalis* and Acinetobacter were encountered in Hammersmith Hospital (Table 9). *Esch. coli* and *Staph. aureus* were the commonest related organisms in each centre. The greater incidence of infection in the London unit cannot be accounted for by different surgical techniques or different approaches to the management of the catheter systems, since these were the same in each unit. Possibly organisms in the London centre are more virulent and therefore are able to establish more easily when a suitable nidus for infection is present.

Short-term antibiotic regimes in this study have shown that urinary tract infection rates after prostatectomy can be significantly improved. A short duration of antibiotic treatment is thought not to give rise to antibiotic-resistant organisms. Short regimes are inexpensive, associated with very few side effects and do not require the patient to continue antibiotic treatment after discharge.

Other infective sequelae of surgery, such as respiratory tract infection, bacteriaemia/septicaemia and wound infection were reduced in each antibiotic-treated group (Table 3). The figures were too small to achieve statistical significance but, in combination with the reduction in urinary infection rates in the co-trixomoxazole and cephalexin groups, further confirm the effectiveness of these antibiotics in short-term dosage. It is suggested, therefore, that in addition to the accepted careful aseptic approach to catheter care, co-trimoxazole in a 3-dose regime may be used successfully in the prophylaxis against urinary tract infection and other infective sequelae of prostatectomy.

Table 9 Organisms Cultured in Urinary Tract Infections

Organism	*Norfolk and Norwich Hospital*		*Hammersmith Hospital*	
	No.	*% total*	*No.*	*% total*
Esch. coli	13	56	11	58
Staph. aureus	2	9	1	5
Enterococci	5	22	0	0
Str. faecalis	0	0	3	16
Acinetobacter	0	0	4	21
Pseudomonas	1	4	0	0
Proteus	2	9	0	0
Total	23	100	19	100

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The Management of Acute Retention of Urine

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Summary—In a one-year study period, 134 men presenting with retention of urine due to prostatic hypertrophy were catheterised and sent home, subsequently to be readmitted for prostatectomy. Their progress is compared with that of 176 men who underwent "cold" prostatectomy during the same period.

It is usually advised that patients who present with acute retention of urine should be admitted to hospital, catheterised and prepared for operation within the next few days (Blandy, 1976). Initially for reasons of expediency rather than deliberate choice, this has not been our practice during the past few years. Patients who are referred to the urological service in Stoke-on-Trent with acute retention are, in general, catheterised in the accident unit and sent home, to be admitted at a later date. This practice is quite widespread in the United Kingdom and so, in order to determine whether this is harmful from the patient's point of view, we carried out a comparative survey. Ideally the comparison would have been made between patients catheterised and sent home and those admitted for catheterisation and operation. This was not possible, so the comparison is between those catheterised and subsequently admitted and patients who were admitted for prostatectomy having not previously been catheterised—"cold prostatectomies".

Materials and Methods

Information was collected on all patients who had had a prostatectomy in the 12-month period 1 July 1978 to 30 June 1979, 310 men in all. Of these, 134 presented with acute retention and 176 had been seen in the out-patient department and given dates for admission for prostatectomy; in nearly all cases this was within 3 months, there being no waiting list as such. Not all of the patients with retention were dealt with in the accident unit or in medical wards; some had been catheterised by their general practitioner or by the district nurse, while others had developed retention while away from home, typically in a seaside resort, and had been sent home with an indwelling catheter. Where the procedure was carried out in our accident unit, no attempt was made to achieve the level of sterility maintained in an operating theatre. Sterile gloves and a mask were worn but not a gown. In this series urethral catheters were always used; fine bore suprapubic catheterisation is reserved for cases where a urethral catheter cannot be passed and this was not necessary in any of the patients studied. Latex or plastic catheters were usually inserted, but in some cases the district nurse or a general practitioner had used a silastic catheter. On 2 occasions when a silastic catheter had been left in the bladder for more than 3 months (one patient had been catheterised by his general practitioner and had refused referral to hospital; the other had been catheterised after an abdominoperineal resection) solid deposits of calcium salts on the catheter prevented its removal (Fig. 1), necessitating open operation where transurethral resection (TUR) would have been more appropriate.

After catheterisation blood was taken for haemoglobin and urea estimation. A high urea or a low haemoglobin would have been adjudged an indication for admission, but otherwise the patient was sent home with a supply of spigots and catheter drainage bags. Antibiotics were not prescribed unless the patient's previous symptoms suggested infection. Bladder washouts were not advised as a routine but most patients were put in touch with the (male) district nurse, who used his own discretion concerning minor problems with the catheter. The patient was given an appointment for the next urological out-patient clinic.

In the clinic a fuller assessment was performed and any further investigations or treatments were

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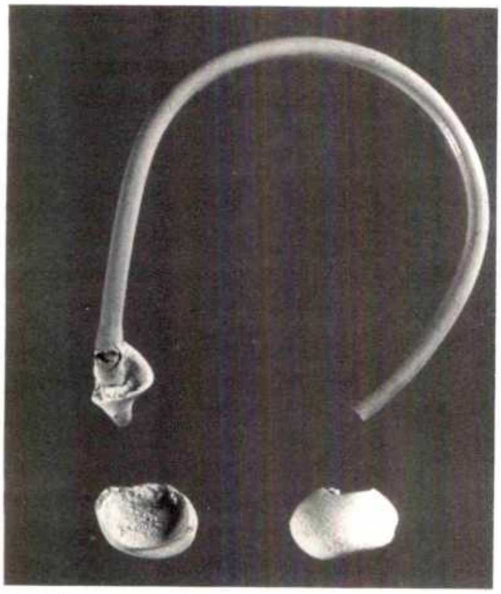

Fig. 1 Solid deposits of calcium salts firmly adherent to a silastic catheter and preventing its removal urethrally.

arranged. An intravenous urogram was not carried out routinely, the only indication for this being haematuria before catheterisation. Those who were thought to be particularly bad risks were advised against operation but were told to come back if the catheter caused trouble; in no case was prostatectomy refused to a patient who wanted it. If the patient gave no previous history of prostatic obstruction and if the episode of retention followed some unusual episode of diuresis (typically induced by the beer consumed at a family celebration) he would be given a date for a one-day admission for a trial without the catheter. If successful, he would be seen at least once more in the out-patient clinic to ensure that all was well. Two patients experienced severe bladder spasms and were admitted urgently for prostatectomy.

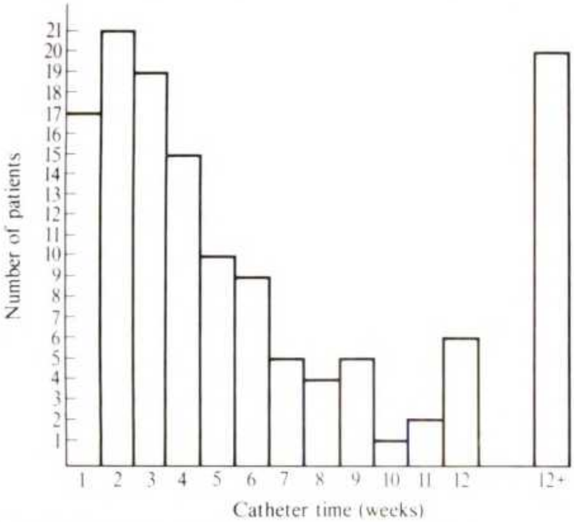

Fig. 2 Patients catheterised for retention of urine.

The aim was to give the patient an admission date no more than 2 or 3 weeks ahead; the extent to which this aim was achieved is shown in Figure 2. Most of the patients waiting 12 weeks or more did so either because it was thought advisable on medical grounds (*e.g.* the development of retention after a myocardial infarction), because the patient had initially refused operation and subsequently changed his mind, or because he had been advised against operation and subsequently found life with a catheter intolerable. Occasionally, the patient himself deferred operation in order to take a previously arranged holiday or to attend some important function. Operation lists were curtailed at times because of the various industrial disputes which took place during the year and this resulted in some patients having to wait longer than would otherwise have been the case. In 2 cases a history of haematuria led to the discovery of a renal carcinoma and this was dealt with prior to prostatectomy.

Patients were usually admitted on the day before operation or, in cases where pre-operative medical treatment was required, 2 days before operation. When it could be arranged, fit patients were admitted on the day of the operation.

In the great majority of cases general anaesthesia was used but in patients with extreme respiratory distress a spinal anaesthetic was given. In principle, the prostate was resected transurethrally if its weight was thought to be 50 g or less, but in some instances smaller prostates were enucleated, sometimes because the size of the prostate had been misjudged and sometimes on account of the surgeon's lack of experience in transurethral work. In no case was vasectomy performed. On 5 occasions a coincidentally discovered bladder tumour was also resected. The catheter was kept clear by continuous irrigation with saline and was removed on the second post-operative day unless bleeding persisted. Antibiotics were given only if clinically indicated (*i.e.* pyrexia) while the catheter was *in situ* and on the results of urine cultures when the catheter had been removed. The patient was discharged as soon as he was passing urine with good control and had an acceptable degree of pain and frequency. Ideally he was discharged on the third post-operative day and this was usually possible in the active patient who made good progress.

Results

A comparison of the make-up of the 2 groups is given in Table 1. It will be seen that patients with retention were usually older, had larger prostates and hence more often open operations, and were more likely to have prostatic carcinoma. Operative complications are listed in Table 2. The death in the retention group was a 76-year-old who died 3 days post-operatively, mainly as the result of haemorrhage. In retrospect it seemed likely that there was a defect in the clotting mechanism; the pre-operative catheterisation was not thought to have been a factor. The other patient (aged 73) died at home 3 weeks after a Millin's prostatectomy. At post mortem examination the cause of death was given as "purulent pericarditis".

It would be difficult to draw any conclusions from so few deaths and therefore a retrospective analysis of post-operative deaths during the years 1974 to 1977 inclusive was performed. In this time 1014 prostatectomies were carried out, with 12 deaths (1.18%) occurring from 1 day to 3 weeks after operation, mostly as a result of cardiac or pulmonary problems. Five of these 12 patients (42%) had been catheterised in the accident unit, sent home and readmitted from 3 to 8 weeks later. Figures are not available to show how many of the 1014 patients had been treated in this way, but the population served and the treatment policy were unchanged between 1974 and 1977 and July 1978 to June 1979, so it is probable that, as in the latter period, some 43% of the total number of cases had been catheterised and subsequently readmitted. If this is so, the risk of mortality in this group differed little from that following a "cold" prostatectomy. Craigen *et al.* (1969) found a similar incidence of retention in a study of the natural history of prostatic disease.

Table 1

	Retention group	*"Cold" prostatectomies*
Number	134	176
Mean age	72.95 yrs (range 54-93)	66.82 yrs (range 44-82)
TUR	106 (79%)	159 (90%)
Mean weight resected	17.26 g (range 4-50 g)	14.2 g (range 3-47 g)
Open prostatectomy	28 (21%)	17 (10%)
Mean weight enucleated	80 g (range 19-346 g)	69.2 g (range 20-150 g)
Carcinoma	15%	7.95%

Table 2

	Retention group	*"Cold" prostatectomies*
Number	134	176
Mortality	1 (0.75%)	1 (0.57%)
Epididymitis	3 (2.2%)*	3 (1.7%)
Severe haemorrhage†	5 (3.7%)	9 (5.1%)
Post-operative stricture‡	1 (0.7%)	11 (6.25%)
Urinary infection§	66 (49.25%)	37 (21%)
Bacteriaemia‖	3 (2.2%)¶	7 (4%)
Suprapubic leakage or serious wound infection	5 (18%)	3 (17%)

* Two of these occurred pre-operatively.

† Post-operative haemorrhage bad enough to necessitate return to theatre or secondary haemorrhage of sufficient severity to warrant readmission.

‡ Patients who complained of symptoms suggesting the presence of a stricture and who were found to have a stricture on dilatation

§ A urine culture was taken at catheterisation, at operation, on removal of the catheter, at the post-operative visit or at other times if symptoms suggested infection. A bacterial count of more than 1 × 10^5 on any of these specimens was taken to indicate a urinary infection.

‖ Not all of these patients had a positive blood culture but all had a high fever and a fall in blood pressure.

¶ Includes one patient who later developed a *Str. faecalis* subacute bacterial endocarditis, probably the result of operation.

Allowing for the fact that the men who had had retention of urine were older and more likely to have social problems, our treatment policy did not appear to result in a more lengthy post-operative stay in hospital in this group of patients (Table 3).

Discussion

The traditional practice of admitting all cases of acute retention of urine presumably dates from the era when the presence of an indwelling catheter required a great deal of nursing care and usually brought misery to the patient. However, with the advent of the balloon type of catheter made from a material (plastic, latex or silastic) which causes little bladder or urethral irritation, an indwelling catheter need no longer hold any terror for the patient or those around him (Ferrie *et al.*, 1979). If a good district nursing service is available, there is no reason why a patient should not be at home

Table 3 Post-operative Stay in Hospital (Mean Number of Days)

Control	TUR	6.12
	Open	8.9
Retention	TUR	6.3
	Open	9.9

and, if he was active before catheterisation, why this level of activity should not be maintained.

Infection is almost inevitable after the first few days of catheter drainage but in most cases this is not a problem and chemotherapy is not necessary. The most troublesome short-term problem is that of bladder spasms; in the long term, encrustation on the catheter or stone formation can lead to pain and haematuria. If the catheter is left on continuous drainage, contraction of the bladder may lead to leakage around the catheter and pain. However, in patients awaiting prostatectomy, the duration of catheter drainage should not be long enough for these problems to occur.

Even though urinary infection rarely troubles the patient with an indwelling catheter, it might be thought that the presence of bacteria in the urine will lead to problems when operation is performed. This was not our experience. As shown in Table 2, a high proportion of patients with retention had urinary infection at some stage and in most of these the urine was infected at the time of operation, whereas most of the "cold" cases came to theatre with a sterile urine. Despite this, the incidence of (clinical) bacteriaemia was lower in the former group and wound infections occurred with equal frequency in both groups. Would it be too naive to suppose that the patient who has had bacteria in his urine for a few weeks has developed antibodies to those bacteria and thus possesses a resistance not shared by the patient into whose bloodstream bacteria must sometimes be introduced, whatever precautions are taken, at a "cold" prostatectomy?

Another problem which might be thought likely to occur after catheter drainage is haemorrhage due to cutting through inflamed tissues. In fact, in most cases the bladder and posterior urethra were not particularly inflamed and, as shown in Table 2, haemorrhage was no more a problem in the retention cases than in the controls. The death as a result of haemorrhage did not appear to be caused by the catheter and the operation itself was not complicated by extensive blood loss. The bleeding became severe some hours later, was accompanied by gastrointestinal haemorrhage and appeared to be caused by an undiagnosed defect in the clotting mechanism.

The incidence of other complications did not point to any particular risk resulting from delay in operation; indeed it seemed possible that an indwelling catheter before operation reduced the risk of developing a urethral stricture. None of the patients with an indwelling catheter died while awaiting operation, although this could occur in an elderly population.

Comfort, or lack of it, is not a thing which can be measured, but there were remarkably few complaints from the patients with indwelling catheters. As had already been mentioned, intractable bladder spasms were occasionally so painful that the patient had to be admitted urgently and treated by operation. Every patient in the series was pleased to be rid of his catheter, but for the man with retention of urine the period of maximum discomfort is that prior to catheterisation; passing the catheter brings relief which lasts even if the catheter is left indwelling. Many patients were pleased to be able to leave hospital and to carry on their normal activities, and there were few complaints even from those who had been led to expect admission by the referring doctor. Quite clearly, if the patient is uraemic and catheterisation is likely to lead to sodium loss problems, admission is essential. In practice, however, patients with chronic retention do not usually present in the accident unit as emergencies.

From the organisational point of view there are considerable advantages in delaying admission. The flow of emergency cases, acute retention of urine included, is inevitably uneven, so that if all such cases are to be admitted at once and put on to an operating list within the next few days, beds must be kept empty and operating time made available. It is obvious that whatever the advantage in maximising the use of beds and operating time, the interests of the patient must come first. We believe we have shown that, in the majority of cases, a man with retention is just as well served by being catheterised, sent home and subsequently admitted for operation as if he is admitted for catheterisation and operation some days later.

No disadvantage was suffered by the men with acute retention and it is concluded that this policy of management is not inferior to the traditional method. The reduction in the number of emergency admissions thus achieved allows a much better use of beds and operating time.

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Reimplantation of the Ureter in Prostatic Carcinoma Associated with Bilateral Ureteric Obstruction

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Summary—Bilateral ureteric obstruction from prostatic carcinoma is not uncommon. A number of techniques for urinary diversion have been used in selected patients when uraemia develops.

Reimplantation of the ureter(s) as an alternative to urinary diversion has been carried out in 21 patients over a 7-year period. In 6 of these patients bilateral reimplantation was done. In another 6 patients reimplantation of the ureter was not possible and cutaneous ureterostomy was carried out. The overall survival time was 10.6 months. In 13 patients living more than 6 months post-operatively, survival time was 1.8 years.

Most patients had severe uraemia and advanced (clinical stage III or IV) prostatic carcinoma. The immediate management of these patients is outlined and the importance of early diagnosis is stressed. It is concluded that, whenever possible, ureteric reimplantation should be considered for relieving ureteric obstruction in patients selected for active treatment.

The clinical management of the prostatic carcinoma patient with bilateral ureteric obstruction associated with uraemia presents a difficult decision on whether to intervene and perform urinary diversion or let the uraemia progress to death.

Urinary diversion can be performed in a number of ways. Percutaneous pyelostomy or nephrostomy can be carried out. As the obstruction of the ureters in prostatic carcinoma in most patients is located close to the bladder, cutaneous ureterostomy or ureterostomy *in situ* is an alternative.

We report our experience with reimplantation of the ureters for bilateral ureteric obstruction with emphasis on the prognosis for these patients afer such a procedure.

Patients and Methods

The records of 27 patients with prostatic carcinoma and bilateral ureteric obstruction treated at our clinic over the period 1971 to 1978 were reviewed. Their mean age was 69.7 years (range 55-83). The primary diagnosis was achieved by fine needle biopsy in 13 patients and by perineal biopsy in 7. In the remaining 7 patients histological examination of transurethrally resected material from the prostate in 4 patients, or transvesically enucleated adenoma in 3 patients, established a diagnosis of prostatic carcinoma. The length of tumour history is illustrated in Figure 1.

At the time of diagnosis the prostatic carcinoma was highly differentiated in 4 patients, moderately differentiated in 8 and poorly differentiated or anaplastic in 9. In 6 patients no classification of the tumour grade was given by the pathologist.

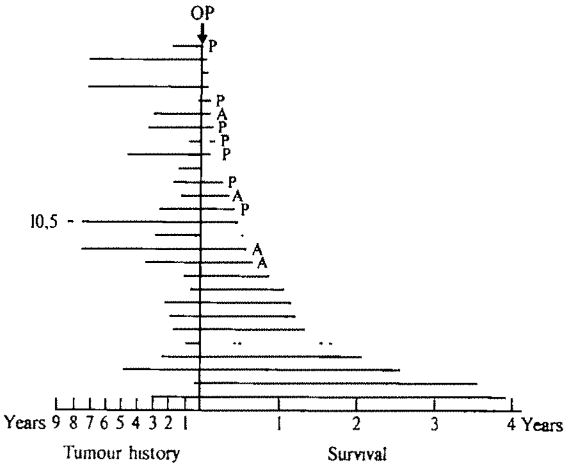

Fig. 1 Surgical procedure for alleviation of ureteric obstruction from prostatic carcinoma, tumour history before and survival after operation in 27 patients
——— Reimplantation.
· · · · · Cutaneous ureterostomy.
P = Percutaneous pyelostomy before surgery.
A = Alive.

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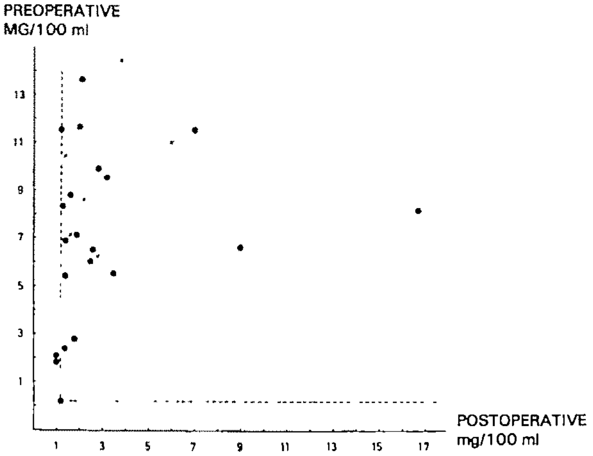

Fig. 2 Pre-operative and 1 month post-operative serum creatinine in 27 prostatic carcinoma patients with ureteric obstruction.

● Ureteric reimplantation (21 patients).

x Cutaneous ureterostomy (6 patients).

- - - - - Upper normal serum creatinine level (1.2 mg/100 ml).

Metastasis, judged by X-ray skeletal survey or isotope bone scan, was seen in 16 patients at the time of diagnosis.

Twenty-six patients were treated with oestrogens before relief of the ureteric obstruction. Seven of these patients were also treated with orchiectomy. Because of prostatic obstruction transurethral resection was carried out in 13 patients prior to relief of the ureteric obstruction.

Most of the patients were severely uraemic (Fig. 2) and often either oliguric or anuric. The mean serum creatinine before surgery was 6.4 mg% (range 1.2-14.4). However, from the information provided by earlier intravenous urography (IVU) in 22 patients, or from the results of an emergency IVU in 5, a non-functioning kidney was diagnosed in 16 patients. The results of these pre-operative IVUs are shown in Table 1.

Renograms were carried out in 8 patients. There were 9 functioning kidneys, 5 right and 4 left. Seven kidneys were non-functioning and delayed excretion consistent with hydronephrosis was seen in 6 kidneys, 3 on each side. Only 3 kidneys had a normal renogram curve.

Table 1 Results of the Last Pre-operative IVU in 27 Patients with Ureteric Obstruction Caused by Prostatic Carcinoma

IVU findings	*Right*	*Left*	*Total*
Normal kidney	6	4	10
Minimal hydronephrosis	1	3	4
Moderate hydronephrosis	3	5	8
Marked hydronephrosis	7	7	14
Non-function	8	8	16
Number of renal units	25*	27	52

* Two patients previously nephrectomised.

The ureteric obstruction was treated in 21 patients by reimplantation of the ureter; in 6 the reimplantation was bilateral. In 15 patients with a non-functioning kidney unilateral implantation only was carried out (Table 2). Reimplantation was performed using a simple technique that did not prevent reflux. The dilated ureter was in most cases sutured to the bladder mucosa with 2 continuous 4/0 catgut or polyethylene-glycol sutures. In all patients the upper urinary tract on the implanted side was drained by a baby-feeding tube for 10 days; this was taken out through the bladder and the abdomen via separate incisions. A Foley bag catheter was used for draining the bladder. A percutaneous pyelostomy was performed in 7 patients before surgery (Fig. 1). In 6 patients in whom the pre-operative examination with cystoscopy and bimanual palpation under spinal or general anaesthesia revealed extensive tumour involvement in the pelvis, a cutaneous ureterostomy was performed (Figs. 1 and 2).

Twelve of 27 patients were admitted with an indwelling bladder catheter. Five of them died post-operatively. Of 22 discharged patients 12 had bladder catheters. Post-operatively, a transurethral resection was carried out in 5 patients in order to relieve prostatic obstruction. Four of these were discharged without a bladder catheter.

Post-operatively, one patient was given radiation therapy in a curative dosage. Another 7 patients were given palliative radiation therapy because of bone metastases.

Results

In 21 patients subjected to reimplantation of the ureter, serum creatinine was assessed post-operatively (Fig. 2). One month post-operatively serum creatinine values averaged 2.9 mg% (range 1.0-

Table 2 Operation for Alleviation of Ureteric Obstruction in 27 Patients with Prostatic Carcinoma

	Right	*Left*	*Bilateral*	*Total*
Reimplantation	6	9	6	21
Cutaneous ureterostomy	3	3		6
Percutaneous pyelostomy before surgery	4	3		7

16.7). In 19 patients there was a decrease in serum creatinine and in 2 patients serum creatinine values returned to normal. One patient had a normal serum creatinine value pre-operatively but had a marked unilateral hydronephrosis and a contralateral non-functioning kidney. In one patient progressive deterioration of kidney function, judged by serum creatinine, ensued.

All patients subjected to cutaneous ureterostomy showed improved renal function as judged by serum creatinine. IVU was performed in 12 patients after surgery but not in 15 because of high serum creatinine levels. Post-operative IVU in 8 patients subjected to reimplantation of the ureter(s) showed improved function in 4 patients, unchanged in 3 and a deterioration of kidney function in one. In 4 patients subjected to cutaneous ureterostomy renal function improved as judged by IVU in 3 patients and deteriorated in one.

Figure 1 shows the tumour history before and survival after the surgical procedure chosen for alleviation of ureteric obstruction. Eighteen patients had a tumour history of more than 2 years. The overall survival time was 10.6 months. In 13 patients living more than 6 months post-operatively the average survival was 20 months. Only 4 patients remain alive and in these cases the operation has been carried out over the last 8 months.

An autopsy has been carried out in 15 patients. Uraemia was regarded as the cause of death in 4 patients. In all instances autopsy revealed widespread disease with metastases to lymph glands and bone. Soft tissue metastases were also seen in the lungs and liver in 2 patients. Involvement of the abdominal wall was seen in one patient and the brain in another. Severe pyelonephritis was seen in 2 patients.

Discussion

Between 1968 and 1972 1171 patients with prostatic carcinoma were diagnosed in the urban-rural area in which our hospital is located. All patients were filed by the Cancer Registry of the National Board of Health and Welfare. It is estimated that another 1200 to 1400 patients with prostatic carcinoma were diagnosed over the years 1972 to 1978 (actual figures not available), which probably means that only about 2% of patients with prostatic carcinoma were seen at our hospital with bilateral ureteric obstruction and, in most instances, uraemia. This figure is probably higher, many patients not being admitted since their uraemic state has been regarded as a terminal event.

Prostatic carcinoma as a cause of ureteric obstruction is not uncommon. Unilateral or bilateral obstruction was seen in 10% of 1065 patients treated for prostatic cancer (Michigan and Catalona, 1977). However, autopsy studies indicate much higher figures. In an analysis of 100 patients dying from prostatic carcinoma, 29 patients had signs of ureteric obstruction (Sigel, 1965).

The status of the upper urinary tracts influences the 5-year survival rate in patients without bone metastases (Ganem, 1957). Treatment with bilateral orchiectomy followed by oestrogens and transurethral resection when indicated resulted in a 54.3% 5-year survival rate in patients with normal upper urinary tracts compared with a 32.4% survival rate in patients where unilateral or bilateral hydronephrosis was seen when treatment was started.

In a review of 34 cases of bilateral ureteric obstruction secondary to carcinoma of the prostate (Khan and Utz, 1975), 14 patients initially presented with uraemia and bilateral ureteric obstruction. Seven patients were treated by urinary diversion with a nephrostomy. In this group 2 patients were alive after 2 and 4 years respectively. The remaining 5 patients died within 5 months. In patients not treated, renal failure was progressive and all died within 3 months, 4 within one week.

If ureteric obstruction is detected in a new patient with prostatic carcinoma, the patient is followed by repeated urography or renograms, and the effect of treatment with regard to the obstruction can be monitored. It has been our policy not to intervene surgically if there is a unilateral obstruction, with the exception of the rare situation where obstructive pyelonephritis develops. This has occurred in only one patient who was operated on after this study was completed. If the patient eventually develops uraemia and an earlier IVU has shown non-function on one side and obstruction on the other, then the latter should be approached surgically for alleviation of the obstruction.

Since many patients suffering from prostatic carcinoma eventually develop ureteric obstruction, it seems important to stress the value of a periodic evaluation of the urinary tract. However, in spite of normal serum creatinine and no symptoms we have often noted that an IVU shows non-function of one kidney and hydronephrosis on the other side.

In a patient with prostatic carcinoma associated with uraemia infravesical obstruction has to be ruled out. A catheter should be passed to the bladder. If urinary retention is obvious and the flow of urine over the next few hours is sufficient, one should wait to see if improvement of renal function, as judged by serum creatinine, ensues. An IVP can be done later in order to evaluate the upper urinary tract. On the other hand, if there is no urinary retention the next step will depend on the state of the patient. If there is progressive uraemia and oliguria, then an urgent evaluation of the state of the kidneys must be made, using radioisotope or ultrasound methods. A percutaneous pyelostomy may be carried out in order to give time to assess the patient and tumour. A cystoscopy with determination of bladder capacity as well as bimanual palpation should be performed on an emergency basis. The patient should be given a general anaesthetic with relaxant or a spinal or epidural block. The extent of tumour involvement of the prostate and the surrounding tissues is important when considering ureteric reimplantation. Passing a ureteric catheter can be tried but may not be successful. In only 2 of our patients was this possible. If the bladder capacity is more than 200 ml, reimplantation of the ureter(s) is recommended and can preferably be done at the same time as the cystoscopy.

If an earlier IVU has shown non-function of one kidney and cystoscopy reveals a small bladder capacity, a cutaneous ureterostomy on the better kidney is recommended, since in these patients the pelvis is often filled with a large tumour mass.

In patients where no information is available regarding the upper urinary tracts and the bladder is not suitable for reimplantation, cutaneous ureterostomies or bilateral ureterostomies *in situ* may be the best way of handling the situation. We prefer a cutaneous ureterostomy rather than a ureterostomy *in situ*, which has the same disadvantages as other procedures using foreign material in the urinary tract such as a nephrostomy or a percutaneous pyelostomy. This leads to problems with infection and catheter clogging, and the catheter also has a tendency to extrude. Patients with a cutaneous ureterostomy can in most instances be taken care of on an out-patient basis. If facilities are available for a percutaneous pyelostomy this can be considered as a temporary or, in some patients, as a definitive procedure.

Ethical considerations have been raised against active therapy in these patients because of their miserable quality of life and the poor effects of urinary diversion (Khan and Utz, 1975). We do not accept patients with known liver or lung metastases for surgery but bone metastases did not influence our decision to alleviate ureteric obstruction.

The surgical approach, if any, to ureteric obstruction in prostatic carcinoma should be decided individually and reimplantation of the ureter(s) should be the preferred procedure. If, however, there is a big tumour mass in the pelvis and/or if the bladder has a very limited capacity, a cutaneous ureterostomy is recommended if possible. The presence of a bladder outlet obstruction does not contraindicate reimplantation of the ureter(s). A transurethral resection of the prostate can be performed later when uraemia subsides. This was actually done in 5 of our reimplanted patients, 4 of whom could be discharged without an indwelling bladder catheter. If such an operation does not lead to an ability to void, the indwelling bladder catheter should simply be kept in place. In our opinion this is easier for the patient and the urologist to handle than a ureterostomy *in situ* or a nephrostomy. Even a cutaneous ureterostomy can be a problem for the patient because of a tendency to stricture formation.

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Urethral Diverticula in the Adult Female

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Summary—Forty female patients with persisting urinary symptoms were investigated using positive pressure urethrography. Sixteen patients were found to have urethral diverticula; 14 of these underwent diverticulectomy. In addition, 17 patients were found to have a markedly distensible urethra on X-ray and only the remaining 7 were deemed normal. The clinical and radiological features and surgical management of these patients are presented.

Female patients with symptoms of recurrent cystitis of no obvious aetiology are commonly encountered in urological practice. Urethral diverticulum as a cause of such symptoms is rarely diagnosed but is probably more common than generally believed. The incidence in asymptomatic females has been reported at 3% (Anderson, 1967) and may well be higher in symptomatic patients.

The aetiology of urethral diverticulum remains obscure. Rare cases have been described in children (Silk and Leibowitz, 1969) and neonates (Johnson, 1938), indicating a possible congenital aetiology, but diverticula occur almost exclusively in young and middle-aged women. The most favoured theory involves a "closed off" infection to a periurethral gland. An abscess is formed which breaks back into the urethra, thereby establishing a connection which may become secondarily epithelialised. Histological data are scarce and inconclusive.

Patients and Methods

Between 1967 and 1977, 40 female patients presented to our urological out-patient department with persisting symptoms of cystitis. When intravenous urography and cystoscopy proved to be within normal limits, these patients were subjected to urethrography using a modified version of the Davis and Cain (1956) catheter. The technique, which has been described elsewhere (Bretland, 1973), is designed to occlude the urethra at both ends while filling it with an aqueous contrast medium.

Forty-six urethrograms were performed on 40 patients. Originally, 17 were thought to have urethral diverticula but on review of the X-rays, one case, for reasons given later, was excluded from this group.

Of the remaining 16 patients, 14 underwent diverticulectomy.

Surgical Technique

All operations were performed by the same surgeon (N.E.S.). The approach was, in all cases, vaginal. A 22 FG Foley catheter was introduced into the bladder, the distended bulb of which indicated the bladder neck. A vertical incision was made in the anterior vaginal wall to expose the urethra. A prolonged search was frequently necessary to identify the diverticulum which was often thin walled and difficult to locate unless chronically inflamed and distended with pus. Bleeding was troublesome at times.

On 2 occasions it was possible to insert the bulb of a Foley catheter (from which the distal part had been removed) into the diverticulum, and distension of the bulb then facilitated dissection.

The defect in the urethra was closely oversewn with plain catgut sutures and the wound closed in layers without drainage. In cases of clustered diverticula around the bladder neck, where the bladder mucosa was opened, a simple suture was sufficient to effect closure.

A Foley catheter was left *in situ* for 7 to 10 days following the operation. Post-operative discomfort was minimal and in no case was there either leak or fistula formation.

Results

Ten patients (71%) had marked symptomatic

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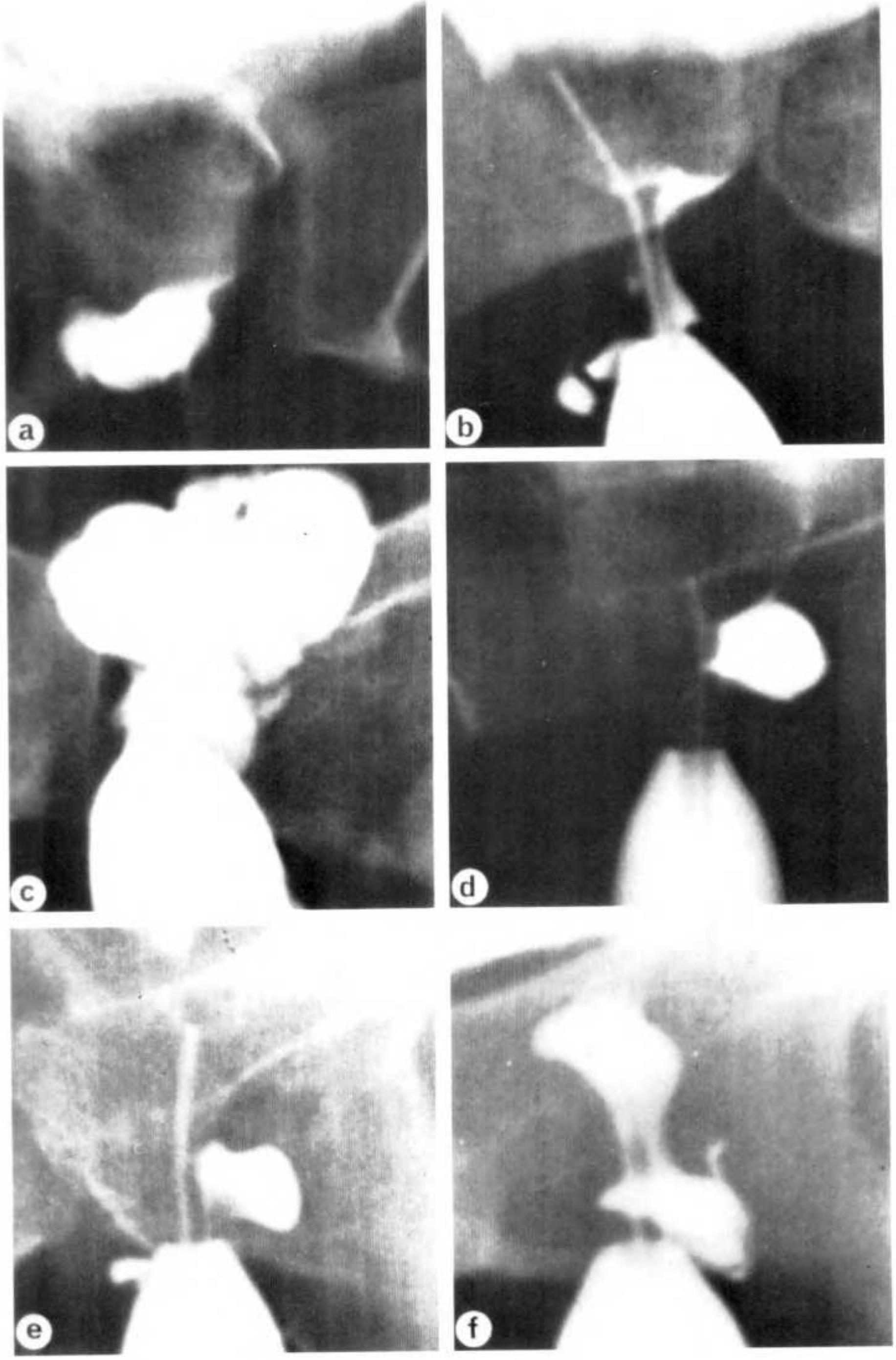


Figs. 1a-f

relief and were delighted with their operation. One patient had a fair result, being left with only minimal residual frequency.

Three patients had a poor result, *i.e.* no symptomatic relief. One was 71 years old and was found on subsequent videocystometrogram studies to have an incompetent bladder neck, probably secondary to cerebral atheroma. Another patient had a strong psychiatric history and the third, a multipara with a history of 4 miscarriages, complained mainly of stress incontinence.

These patients' poor results probably reflect injudicial selection.

Radiological Findings

On the basis of radiological appearances we have divided our patients into 3 groups:

Group I	Urethral diverticula	(16 patients)
Group II	Distensible urethra	(17 patients)
Group III	Normal urethrogram	(7 patients)

Group I: Urethral Diverticula The diagnosis of urethral diverticulum was made on the following criteria:

(1) On adjusting the pressures correctly, a localised rounded collection of contrast medium appeared under the fluoroscopic screen, usually posterolateral to the urethra.
(2) This apparent space had a neck which was narrower than the widest part of the opacity.
(3) On release of pressure, the contrast medium remained in place for at least a few seconds before draining out.
(4) In some cases the margins were irregular or had tracks leading from them.

Originally, the diagnosis of urethral diverticulum was made in 17 patients. One of these patients was explored surgically. No diverticulum was found and the patient experienced no relief of symptoms. On review of her X-rays, it was felt that this may not have been a true diverticulum, but rather a variety of distensible urethra. She has been included in Group II and excluded from the analysis of surgical results.

Two patients, originally described as having "wide mouthed" and "shallow" diverticula, did not undergo surgery. They have been included in the analysis of Group I patients, but could also be considered as having another form of distensible urethra.

This leaves 14 proven cases of radiologically diagnosed urethral diverticula, of which 12 sets of films were available for retrospective review. The radiological appearances were of 3 types:

(1) Diverticulum of the proximal urethra (3 on the left and 5 on the right, all close to the bladder neck).
(2) Diverticulum of the distal urethra (2 cases, both on the right and extending down posterolaterally).
(3) Diverticulum extending in a ring-like track around the urethra (2 cases).

Examples of the first 2 types are shown in Figures 1a and b.

The diverticula were not shown either on intravenous urography or on micturating cystourethrography (the latter technique was abandoned very early in the series) but only by using the technique of occluding both ends of the urethra.

The 2 cases of ring-like track were both seen on intravenous urography. One was also demonstrated on micturating cystography and the other on routine urethrography. One such case is shown in Figure 1c.

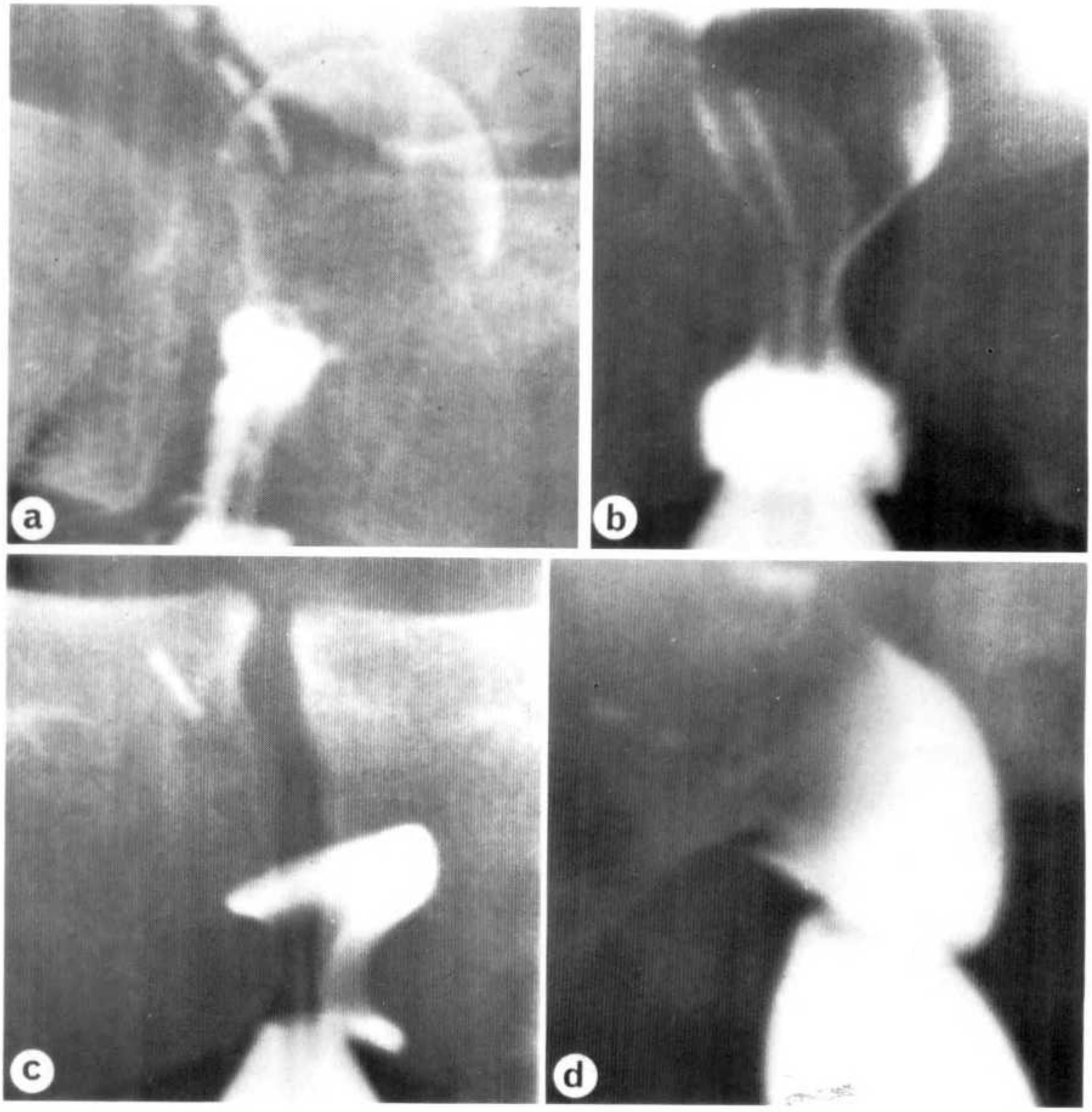
It was sometimes difficult to distinguish between a true diverticulum and a distensible urethra (as described below) and 3 examples of surgically confirmed diverticula which only just fit the radiological criteria are seen in Figures 1d, e and f. Indeed, Figure 1f shows both distensible urethra and distal diverticulum.

Group II: Distensible Urethra In this group of 17 patients, urethrograms appeared abnormal because of asymmetrical collections of contrast medium at the proximal or distal end of the urethra (or both). Several of these were originally described as "shallow", "wide mouthed" or "collar-like" diverticula until it became clear that these appearances were due to localised distension of the urethra. Review of 15 sets of films available showed that there were 4 types:

(1) Proximal distension (6 cases).
(2) Distal distension (5 cases).
(3) Distensible proximal and distal urethra, giving a "spool" or "bobbin" shape (3 cases).
(4) Generally lax and distensible urethra (1 case).

Examples of these 4 types are seen in Figures 2a, b, c and d respectively.

It is emphasised that, in tamponade urethrography, the bladder neck is distorted by the upper balloon, and the urethra by a non-standardised injection pressure. We cannot therefore be sure of the significance of the X-ray appearances in



Figs. 2a-d

this group and we can only document the striking features encountered.

Group III: Normal Urethrograms This included 7 patients showing normal radiological appearances, *i.e.* a relatively narrow urethra that failed to distend with the tamponade technique.

A confusing image was occasionally obtained of a triangular "collar" of contrast medium trapped under the balloon at the bladder neck. Figure 3 shows a normal urethra and the "collar-like" appearance is also seen in Figure 1b.

Results

All patients were examined by the same clinician (N.E.S.). Fair clinical comparison, we feel, can therefore be made between the patients with radiologically demonstrated diverticula (Group I), patients with distensible urethra on X-ray (Group II) and patients with normal urethrograms (Group III).

These 3 groups have been separately analysed from the point of view of age, symptoms, signs, bacteriuria and parity. The average length of

Table Average Age and Age Scatter

	Group I Urethral diverticula	*Group II Distensible urethra*	*Group III Normal*
Youngest	27	18	25
Eldest	74	71	68
Average age at diagnosis	43	39	50

follow-up for the 3 groups was 2.1, 2.0 and 1.9 years respectively.

The age scatter and average age were similar in all 3 groups (Table).

The average duration of symptoms in patients in Group I with urethral diverticula was approximately 5 years. Group II patients had a mean duration of symptoms of 7.9 years, but this may have been falsely extended by one 64-year-old patient who claimed life-long symptoms. In Group III the average duration of symptoms was 1.1 years.

From Figure 4 it can be seen that frequency, dysuria and urgency, in that order, were the predominant symptoms in all 3 groups.

The incidence of dyspareunia was similar in Group I and Group III patients (40 and 50% respectively). A striking feature was the high incidence of stress incontinence in Group II patients.

Only one patient in this study presented with a palpable lump on vaginal examination (Fig. 5). However, nearly half of the women with diverticula exhibited marked localised tenderness over the anterior vaginal wall. This sign was elicited from none of the Group II or III patients.

Twenty-seven per cent of patients in Group I, 13.3% in Group II and 33.3% in Group III had a significant bacteriuria. These figures were based on random urine samples taken in out-patients and not necessarily when the patients were symptomatic.

Eighty per cent of the patients with urethral diverticula were multipara. Approximately half of Group II and III patients had one or more children.

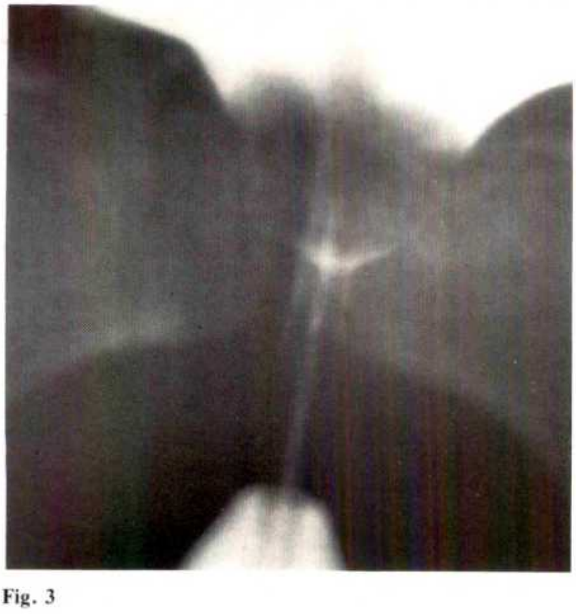


Fig. 3

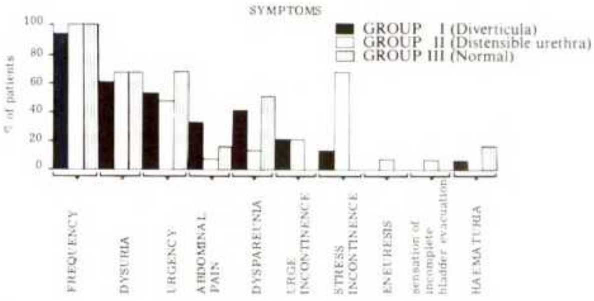


Fig. 4

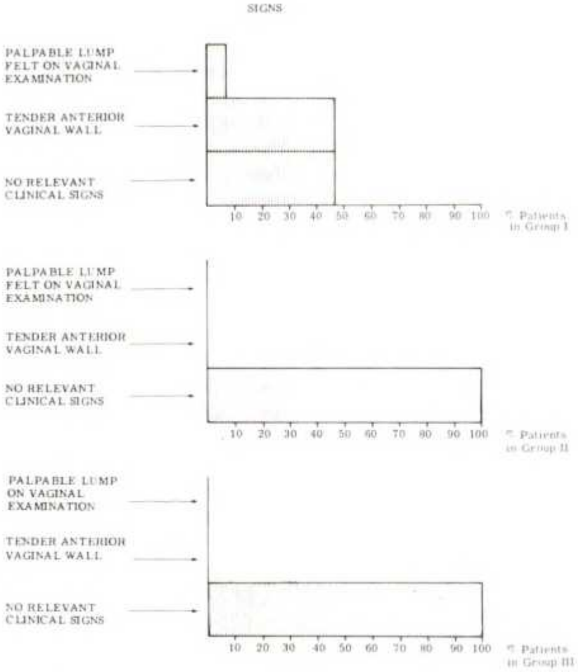


Fig. 5

Discussion

The average age at diagnosis (43 years) of women with urethral diverticula compares closely with that quoted in previous reports, *e.g.* 40 years (Herman and Greene, 1944), 36.6 years (Moore, 1952) and 40 years (Benjamin *et al.*, 1974).

However, as both age and age scatter did not vary greatly between the 3 groups, 40 years may simply represent an average age for a symptomatic female patient presenting to urological outpatients.

An approximate figure of 5 years for the duration of symptoms in patients with urethral diverticula also correlates closely with that of previous reports (Herman and Greene, 1944). Whether this reflects the natural history of the disease or the difficulty in reaching the diagnosis is a matter of speculation.

The predominant features of frequency, dysuria and urgency have been reported by other authors (Davis and Tellinde, 1958: Emmett and Witten, 1971). In this study, the distribution of these symptoms is remarkably similar in all 3 groups and no symptom complex could be said to be diagnostic of urethral diverticulum.

A 40% incidence of dyspareunia in Group I patients was not unexpected, but we cannot explain the 50% incidence in patients with normal urethrograms.

Localised anterior vaginal wall tenderness was the most striking clinical sign elicited in patients with diverticula. Only one case presented with a palpable lump.

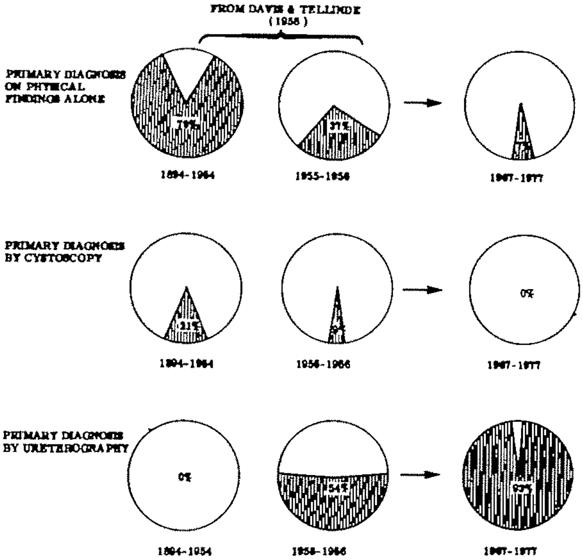


Fig. 6

Herman and Greene (1944) described the majority of diverticula as being the size of an "English walnut", Wharton and Kearns (1950) reported that in almost all of their cases the diverticula were between 1.5 and 5 cm in diameter.

It seems surprising that Group III patients should have had a higher overall incidence of bacteriuria than those in Group I, where a definite abnormality would seem more likely to predispose to urinary tract infection. We suspect that these statistics are misleading.

Here again, comparison with older literature is interesting. In 1950 Wharton and Kearns reported a 100% incidence of bacteriuria, 10% of which were gonococcal. Davis and Tellinde (1958) found that, in 63% of their cases, pus could be expressed from the external meatus on "stripping" the urethra.

It has been suggested that the trauma of childbirth plays a part in the aetiology of urethral diverticula and, indeed, 80% of Group I patients were multipara. A much larger series (Davis and Tellinde, 1958), however, has reported a decreasing incidence of diverticula with increasing parity.

Our series portrays the patient with urethral diverticulum as a middle-aged multipara with long-standing symptoms of recurrent cystitis and little in the way of physical signs other than localised anterior vaginal wall tenderness. If this is indeed a representative portrayal, there would appear to be a "changing face" to the presentation of this disease in that we are no longer encountering the more obvious symptoms and gross physical signs described in earlier reports.

The reason for this change may lie in the ready availability of effective antibiotics to such patients via their local medical services. Periurethral abscess formation is prevented and subsequent overt disease masked.

From Figure 6 it can be seen that, whereas diagnosis of urethral diverticula by physical examination and cystoscopy is made with decreasing frequency, radiology takes on an increasingly important diagnostic role.

We have noted a high incidence not only of diverticulum, but also of distensible urethra, using the described technique of tamponade urethrography. The latter radiological entity may well correspond to a weakness of the bladder neck musculature or periurethral supportive tissue, a theory supported by the high incidence of stress incontinence found in Group II patients. We would have liked to follow up these Group II patients with videocystourethrography (Campbell and Sniderman, 1976), since it is important to distinguish the radiological appearances from that of the diverticulum to exclude false positives.

Having once demonstrated a diverticulum which has given rise to symptoms, the consensus of opinion favours surgical excision (Johnson, 1938; Benjamin *et al.*, 1974) despite the reported incidence of urethrovaginal fistula (Henessy, 1958). Using the surgical technique described, we have found diverticulectomy to be a simple and effective procedure, free of complications.

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Detection of Urethral Incompetence. Erect Studies Using the Fluid-Bridge Test

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Summary—The fluid-bridge test (FBT) detects the entry of urine into the proximal urethra during coughing. In this study it was applied in the investigation of incontinent patients when they were first supine and then standing up. The test results in 76 women with urinary incontinence and 27 women with normal urinary control are reported.

When the test was performed erect at 0.5 cm from the urethrovesical junction, it was positive in 68 (90%) of the study group and 4 (15%) of the controls. The difference between the results in the 2 groups is highly significant ($P<0.001$).

In 12 (16%) of the incontinent group the test at 0.5 cm became positive only when the subject was standing up, indicating that erect testing adds to the diagnostic efficiency of the method.

Erect testing seems more relevant to the investigation of stress urinary incontinence. This study has shown that this is possible using simple urodynamic apparatus.

The fluid-bridge test can detect the entry of urine into the proximal urethra during stress (Brown and Sutherst, 1979). Thus far, the test has been used in supine patients only (Sutherst and Brown, 1980). In this paper we report our first series of results using the test in patients who were standing up during the procedure.

Patients and Method

One hundred consecutive female patients attending an incontinence clinic for urodynamic assessment* of their symptoms were studied (mean age 51.5 years; mean parity 3.3). Twenty-seven women with normal urinary control were also tested (mean age 40.6 years; mean parity 1.7). These were women attending hospital for investigation of abnormal uterine bleeding or infertility.

After cystometry the bladder volume was reduced to 150 ml. This was a volume large enough to enable clear definition of the urethrovesical junction during measurement of the urethral closure pressure profile (UCPP), yet small enough to cause neither discomfort nor bladder contractions in most patients (even in those with bladder instability). The UCPP was recorded by the method of Brown and Wickham (1969) with the patient supine. The FBT was then performed. The method has been described in detail previously (Brown and Sutherst, 1979). A positive test result

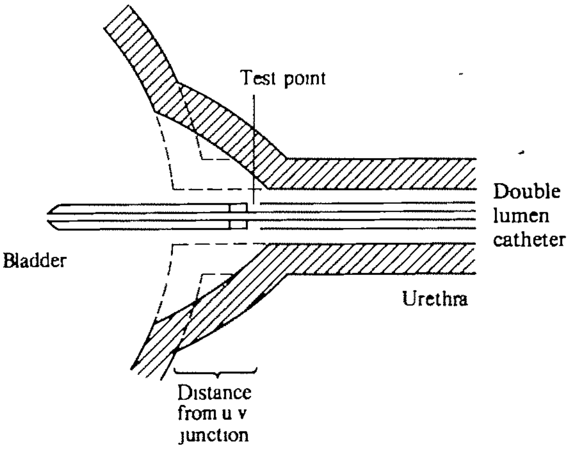

Fig. 1 Diagram showing double lumen catheter and test point in the proximal urethra. During a cough the urethra may open to allow fluid to surround the catheter side holes (as in the diagram).

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* In this paper all methods, definitions and units conform to the standards proposed by the International Continence Society (1976) except where specifically noted For all urethral pressure tests zero reference point was the upper border of the symphysis pubis.

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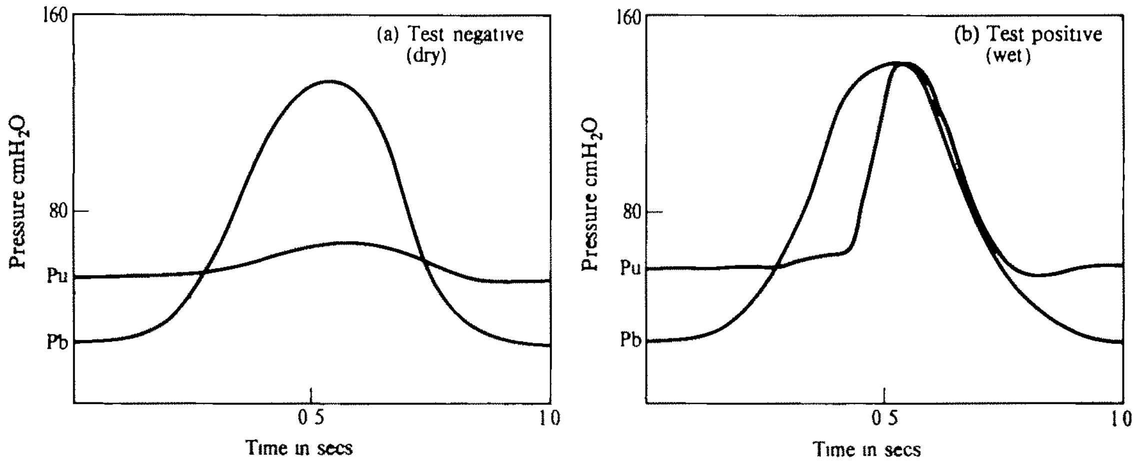

Fig. 2 Typical negative and positive FBT results. Pressure tracings of polaroid photographs of CRT screen recordings: (a) the urethra remains closed (b) the urethra opens as far as the test point

depends on the establishment of a fluid-bridge between the bladder and the urethral test point during a cough cycle (Fig. 1). If this happens, pressures recorded at the 2 points momentarily become equal. The form of bladder and urethral pressure tracings displayed on a pen recorder (with a paper speed of 5 cm/s) or on a CRT screen indicates whether the proximal urethra has opened. Typical negative (dry) and positive (wet) results are shown in Figure 2. Catheter position is indicated by reference to the UCPP on the paper tracing (Fig. 3).

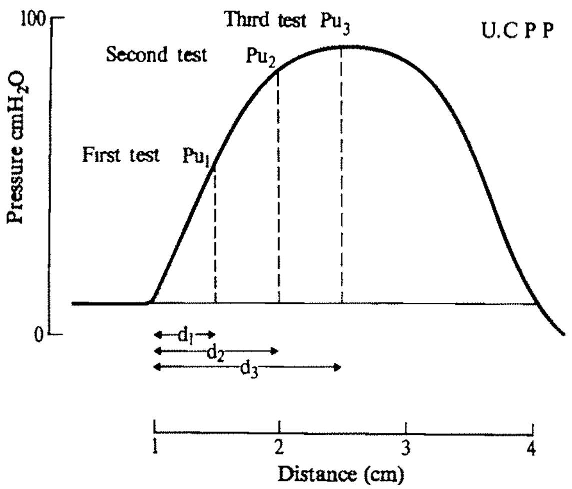

Fig. 3 Diagram showing test point location Pu$_1$ = urethral pressure at first FBT point; d$_1$ = distance of this point from uv junction. Pu$_2$ = urethral pressure at second FBT point, etc. The first point selected is approximately 0.5 cm from the uv junction.

The FBT was first performed at 0.5 cm from the urethrovesical junction (as defined on the UCPP). If a positive result was recorded the test was repeated further down the urethra until a dry point (a negative fluid-bridge test) was reached. By restarting the infusion, and by reference to the UCPP, the position of the catheter side holes could be identified at any time. The patient was then tilted to the erect position on a motorised bed. To prevent movement due to its weight and connections, the catheter was held in position by a clip at the external meatus. The device used consisted of a spring paper clip fixed to a flexible ring pessary (Portex Ltd., Hythe, Kent) held between the patient's thighs (Fig. 4).

If the FBT was now positive, it was repeated at intervals down the urethra to see whether or not

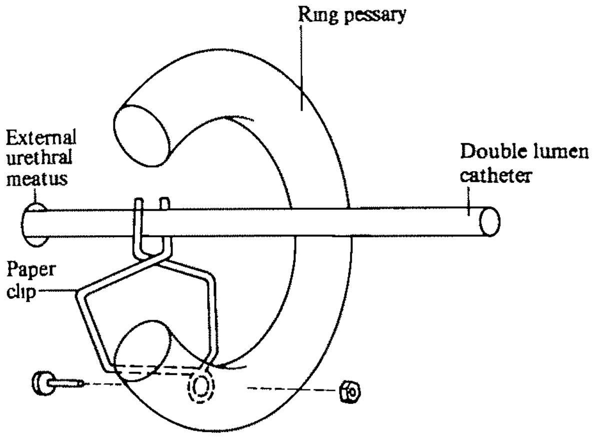

Fig. 4 Diagram of the holding device. A spring paper clip is fastened to a flexible ring pessary.

a cough competent (dry) point could be detected at a lower urethral level.

Finally, the UCPP was measured again to provide another "map" for the identification of the previous catheter locations, in the same way as it was used with the patient supine (Fig. 3).

Other information collected from this study included the following:

1. Clinical evidence of stress incontinence (namely visible urine loss during coughing with the patient either supine or erect);
2. assessment of urethral incompetence from UCPP data;
3. evidence of bladder instability;
4. the overall urodynamic diagnosis.

Results

Of the 100 patients, 24 were excluded from the analysis of the results. Seven of these had recently been operated on for incontinence, and their other urodynamic data (with which the FBT was to be compared) were still abnormal, though they were now continent. In 7, technical difficulties were encountered, either because infirmity of the patient prevented erect testing or because of problems with the apparatus (in one patient the catheter was coughed out). In 10 patients the change from supine to standing position initiated detrusor contractions, making interpretation of the FBT impossible.

Seventy-six patients remained in the study group. In these and in the 27 controls, the results of the FBT were compared with clinical evidence of stress incontinence and with evidence of sphincter weakness provided by other urodynamic investigations (Figs. 5 and 6). All results are discussed in relation to the FBT at 0.5 cm from the urethrovesical junction unless otherwise stated.

None of the control patients had any urinary symptoms. The test was negative in 23 of them and positive in 4. The results were the same regardless of posture. In the 4 demonstrating a positive test at 0.5 cm, the test result was negative further down the urethra.

In the study group the test was positive in 56 cases (73.7%) when the subject was supine (Fig. 5) and in a further 12 (15.8%) when standing up (Fig. 6). The difference in test results between subjects and controls in both supine and erect studies is highly significant.

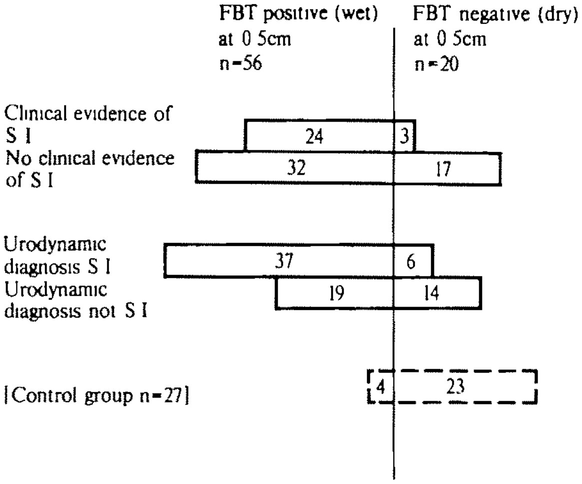

Fig. 5 Results of the FBT performed supine in the 76 patients and 27 controls in the supine/erect study group. SI = stress incontinence.

There were positive tests in 32 and 41 women (depending on whether they were supine or erect) who had no clinical evidence of stress leakage, but provided the test was performed erect there were no negative FBT results in women with demonstrable leakage.

The results of the FBT agreed with the urodynamic diagnosis made from other investigations in 51 of the 76 patients (67%). However, there were 25 incontinent women with a positive erect test at 0.5 cm who had no evidence of urethral incompetence. In 15 of these 25, the test was also positive further down the urethra.

There were no negative FBT results in women with other urodynamic evidence of pure stress incontinence providing the test was performed erect.

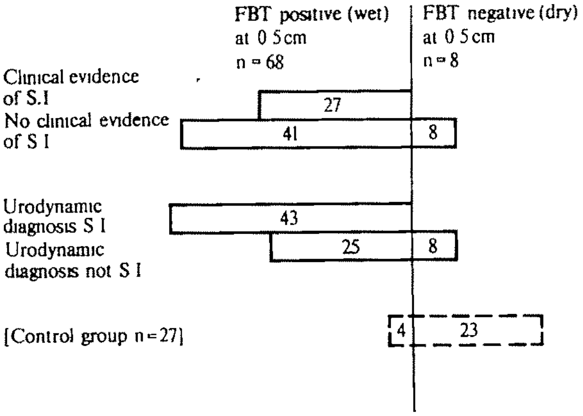

Fig. 6 Results of the FBT performed erect in the 76 patients and 27 controls in the supine/erect study group. SI = stress incontinence.

Discussion

Stress urinary incontinence is more likely to happen when a woman is standing up or when there is a sudden rise in intra-abdominal pressure such as occurs during coughing. Therefore it seems logical to test for incontinence when the patient is standing up and coughing. In this respect the relevance of supine urodynamic tests, without stress, is questionable.

The FBT can be performed using simple apparatus. It can easily be incorporated into a urodynamic testing programme and is not dependent on exact calibrations. This study has shown that it is possible to perform the FBT when the patient is standing up. In only one case early in the series was the catheter dislodged enough for it to fall out. Since that time the holding device shown in Figure 4 appeared to hold the catheter in position satisfactorily. Catheter location could easily be checked before and after each test by reference to the supine or erect UCPP.

Apart from a few cases of bladder instability in which passive posture change initiated a detrusor contraction, and a small number in which there were technical difficulties, the test gave clear results in all of the patients studied.

Twenty-three out of the 27 control patients (85%) demonstrated a negative test very close to the urethrovesical junction. In 4 there was a positive test at 0.5 cm. The FBT was negative below this point in each of these patients. Nevertheless, these women appeared to be normal as far as urinary control and urodynamic testing were concerned. The test point of 0.5 cm was selected because opening of the urethra to this point during coughing appeared to be diagnostically useful in an earlier, supine only, study (Sutherst and Brown, 1980). However, with further experience of this test it may be necessary to fix the level of diagnostic significance further down the urethra.

The test results in the 33 patients with no other urodynamic evidence of stress incontinence may, therefore, include some "false positives" when the test is read at 0.5 cm from the urethrovesical junction. However, there is still a highly significant difference between the test results in this group and those in the control group ($P<0.001$). Furthermore, in 15 of the 25 patients with a positive test at 0.5 cm the FBT was also positive further down the urethra. This suggests that a positive test at 0.5 cm should not be ignored; sequential testing through the length of the urethra is indicated in these cases.

In 12 patients (16% of the incontinent group) the FBT was negative when performed supine, but positive erect. It appears that by performing the FBT erect instead of supine it is easier to establish or confirm the overall urodynamic diagnosis of genuine stress incontinence.

Further studies are needed on the degree/distance of urethral opening which might be considered normal.

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Teflon Tape Suspension for the Control of Stress Incontinence

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Summary—Vaginal surgery for the relief of stress incontinence has a failure rate which is unacceptable. Since 1964 the authors have combined in the management of female urinary disorders. Where surgery was indicated the combined approach was used as the primary procedure.

The bladder neck was elevated by a technique of suspension using 2 mm Teflon tape, via the cave of Retzius. It was not a sling. The results of 100 consecutive operations are presented.

The team approach has led to a better understanding and management of all varieties of female bladder problems.

In this report the junction between the upper urethra and the bladder and the fascia on each side is called the "bladder neck". Whatever the mechanism of stress incontinence of urine in women, the condition is relieved by adequate elevation and stabilisation of the bladder neck. In the late 1940s a success rate of 80% was claimed for adequate vaginal surgery, but it was more likely to have been 50 to 60% (Jeffcoate and Roberts, 1952; Stanton *et al.*, 1976).

Since 1964 the authors have combined in the assessment and management of every woman with bladder problems of any variety, it being agreed that the combined type of operation would be performed as a primary procedure.

The urologist (R.J.C.) decided to employ a procedure whereby a single stitch of 2 mm Teflon tape was inserted into the fascial hammock on each side of the bladder neck, which was pulled upwards into its original anatomical position. The stitch did not run under or encircle the urethra, and thus the disadvantages of sling procedures were avoided.

Patients and Methods

Preliminary Assessment

An accurate history was taken by both the gynaecologist and the urologist separately. The only special investigations performed were routine urine analysis, excretion urography and cystoscopy.

Operation

The patient was placed in Lloyd Davies stirrups with a Trendelenburg slope to the table. The urologist worked above and exposed the cave of Retzius in the standard manner. The gynaecologist sat below.

The suture used for the suspension by the urologist was prepared from a 40 cm length of 2 mm Teflon tape (Braided Tape No. 3777, produced by US Catheter and Instrument Corporation, New York, USA) mounted at each end on a No. 4 or No. 3 Mayo round-bodied needle. It was introduced through the anterior abdominal musculature just above the symphysis pubis and just lateral to the attachment of the rectus muscle. Beginning on the right side, it was taken down to bite into the fascia to the right of the bladder neck and then up again out through the rectus sheath. The left end travelled in a similar manner so that, at the conclusion of its insertion, the 2 free ends could be tied together in a single knot anterior to the rectus sheath (Figs. 1, 2 and 3). The location of the bladder neck and the exact point for insertion of the suture were determined by co-operation between the 2 operators as follows:

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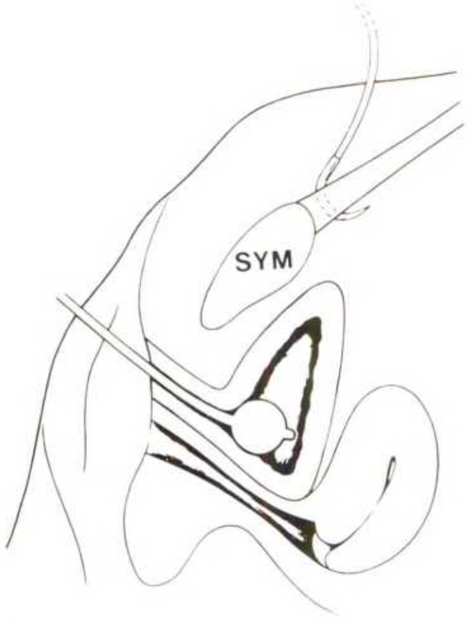

Fig. 1 Beginning of placement of Teflon tape suture through the abdominal wall musculature.

1. The urologist palpated the lower edge of the balloon of a Foley catheter lying within the bladder cavity and pulled downwards by the gynaecologist.
2. The urologist recognised the changeover point of the transverse lower edge of the bladder into the longitudinal ridge of the upper urethra, as defined by the indwelling catheter stem.
3. The gynaecologist inserted a forefinger into the vagina upwards and forwards just lateral and distal to the lower edge of the catheter balloon.
4. The urologist palpated the tip of the gynaecologist's forefinger, the 2 being separated by fascia only if the vaginal epithelium had been opened and turned aside, or by fascia and vaginal epithelium if the latter was intact.

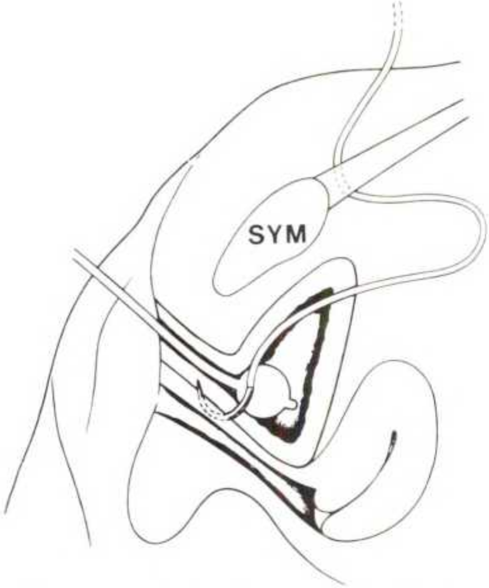

Fig. 2 The needle takes its bite into the fascial "hammock" at the bladder neck.

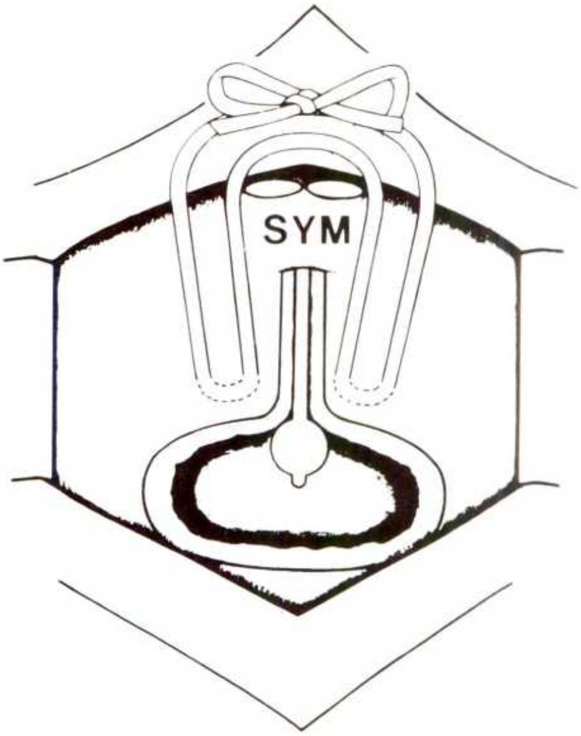

Fig. 3 Both ends of the suture are brought out again through the abdominal musculature and secured by a firm knot.

The urologist inserted the needle firmly into the hammock fascia, thrusting it against the counter pressure of the gynaecologist's forefinger pushing upwards and forwards from below. This was a critical part of the procedure and was easier if the gynaecologist wore a thimble on his finger.

The final tension of the suture was adjusted with care and precision, both surgeons deciding together when the bladder neck elevation appeared correct and equal on each side.

Gynaecological Procedure

The role of the urologist in the operation was clearly defined but the gynaecologist decided what particular gynaecological procedure might also be required.

1. When there was pure stress incontinence and little, if any, uterovaginal prolapse, the gynaecologist did no more than identify the bladder neck and ensure that the suture did not penetrate the vaginal epithelium.
2. If the patient had, in addition to stress incontinence, an uncomfortable cystocele, enterocele or rectocele, it was repaired. If there was discomfort from uterine prolapse, this was repaired.

   If there had been previous vaginal surgery, the gynaecologist mobilised the bladder neck if it was fixed in scar tissue (the frozen bladder neck), but otherwise left it alone.
3. If a patient, in addition to stress incontinence, had dysfunctional or organic menstrual disturbances requiring surgical management, the procedure began with an abdominal hysterectomy. After this was completed the wound was covered with a pack, the patient's legs were elevated into the Lloyd Davies stirrups and the urologist exposed the cave of Retzius.

At this point it is reasonable to make 2 comments regarding the gynaecologist's part in the procedure. Firstly, there is obviously a considerable variation in what he can and should do and he alone makes the decision in this matter. He should free himself from the idea that he has to perform an anterior colporrhaphy and must determine the flow of the operation.

Secondly, if it is necessary to perform significant vaginal surgery, the gynaecologist will not find it comfortable within the confines of the Lloyd Davies stirrups and it is better in these circumstances for him to carry out his part of the operation first, with the patient in the usual lithotomy position. In such cases the vaginal procedure, be it repair or vaginal hysterectomy, is completed to the stage just short of closing the anterior vaginal epithelium beneath the bladder neck. The gynaecologist then waits whilst the lithotomy stirrups are raked "downwards" and the urologist gets in above—through a small Pfannenstiel incision. The 2 surgeons then carry out the combined part of the operation for the relief of the stress incontinence.

Results

This use of Teflon tape suspension was described in 1967 in a short paper presented (by R.J.C.) at the Annual General Meeting of the Urological Society of Australasia in Auckland, New Zealand, but this was not published. A more extensive paper was read at the Eleventh Annual Congress of the Royal College of Obstetricians and Gynaecologists in Perth, Western Australia, in 1975 but this also was not published. In order to obtain sufficient time for follow-up, 100 consecutive patients operated upon between 1966 and 1972 were used for the purpose of statistical study. Patients not needing surgery were excluded from the series; they included patients with post partum stress incontinence, those who considered the degree of incontinence mild enough to be acceptable, and those who responded to pelvic floor exercises.

The 100 patients subjected to surgery were divided into 3 groups:

(1) Those with pure major stress incontinence and no other disturbance of bladder or uterine function.

(2) Those who had a major degree of stress incontinence but who also suffered from other bladder disturbances such as frequency, urgency, urge incontinence or a combination thereof, or significant uterine or pelvic symptoms such as pain or menometrorrhagia.

(3) Those who presented with bladder or uterine symptoms and admitted to stress incontinence on direct questioning. We call this "incidental stress incontinence".

In the 100 cases the proportions shown were 18% pure, 53% mixed and 29% incidental. The full appreciation of this interweaving of gynaecological symptomatology with bladder disturbance has been a major byproduct of these years of teamwork.

Since the patient's subjective definition of her symptom was used before operation, it was also used afterwards to determine success. Whilst the authors would call the "cure rate" 91%, it must be stated that in the remaining 9% who were "significantly improved" there was no patient who was dissatisfied, though it might be argued that by including 29% of patients in whom the stress incontinence was incidental and mild, the figures have been inflated.

No patient was excluded because of age, obesity, heavy smoking, life style or work load. The patients' ages ranged from 31 to 73 years, weight from 50.8 to 95.2 kg (average 65.77 kg). Oestrogen deficiency in post-menopausal women was always corrected before surgery and, if necessary, afterwards, in order to keep the vaginal and bladder base tissues in maximum tonal quality.

Post-Operative Care

The indwelling Foley catheter was left on straight drainage for 7 days. Nearly all patients voided promptly and easily when the catheter was removed.

Complications Considered Due to the Tape

In this series one patient had an infected sinus and one had difficulty in voiding. In both cases the tape was removed through a small incision over the knot. Being a continuous suture it pulled out easily. It did not affect the success of the operation and was not considered a problem.

At the time of this series, urodynamic studies were not available in this city, but since 1975 such studies have been used extensively by the authors and by other gynaecologists and urologists. In retrospect, mistakes in judgement made before urodynamic studies were available were very few, and this is possibly due to the thorough and combined approach in history-taking and examination.

Discussion

Significant improvement in the management of female bladder problems follows routine combined gynaecological/urological management. In the initial assessment this leads to a thorough clarification of the patient's symptoms. This study shows that in only some 20% of women was significant stress incontinence of urine the sole symptom. When combined with other symptoms, those relating to the bladder should be dealt with by the urologist, and uterine or prolapse symptoms should be treated by the gynaecologist.

Throughout the entire programme the patient is kept fully informed about the nature of her problems and the expectations of any proposed management. She may be told that stress incontinence is virtually curable but that frequency and urgency are less simple matters, etc. At all times the patient appreciates that she is under the care of 2 specialists acting harmoniously on her behalf.

For the specific relief of stress incontinence it is recommended that combined surgery be employed. This should be used as a primary procedure in previously untreated patients but is, of course, equally applicable to patients with previous surgical failure.

The concept of suspension of the bladder neck or elevation of the proximal one-third of the urethra is not new (Marshall *et al.*, 1949). The procedure used by the authors is recommended because it is simple and because it employs a non-absorbable non-irritating suture (2 mm Teflon tape) which is placed accurately into the fascia on either sde of the bladder neck and tensioned for correct elevation.

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The Bacterial Content of the Female Urethra. A New Method of Study

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Summary—The distribution of urethral flora has been studied in 30 women, using a new instrument. The results show that significant quantities (>5 colonies) of potential pathogens can be demonstrated in 90% (27) of the patients at the meatus and in only 10% (3) of patients above the midurethral high pressure zone.

Interest in the bacterial content of the female urethra is related to the contamination of mid-stream urines and to the presence of a reservoir of organisms which may be inoculated into the bladder.

Attempts to study the distribution of urethral flora have been associated with a number of interesting instruments. All of these have been aimed at minimising contamination of the proximal urethral cultures from the distal urethra.

In this study a new instrument has been designed for collecting cultures from the proximal urethra.

Patients and Methods

Thirty patients who were admitted for routine diagnostic dilation and curettage were selected for the study of urethral flora.

None of these patients had been admitted for urinary symptoms.

Using the new method, swabs were collected from 2 sites:

1. The distal 0.5 cm of the urethra.
2. 1.5 to 2 cm proximal to the urethral meatus.

The Instrument (Fig. 1)

The new instrument consisted of a sterile cotton-wool swab mounted on a fine metal rod contained within a plastic tube with an external diameter of 2.5 mm. This plastic tube was contained within a further plastic tube 3.5 mm in diameter which was sealed at one end.

The seal was manufactured using a rubber diaphragm with an appropriate opening via a cruciate incision. The elasticity of the rubber was sufficient to maintain a seal while the instrument was being introduced through the urethra for a distance of 1.3 mm. The inner plastic tube was then pushed through the seal for 2 mm. This allowed the cottonwool swab to be introduced into the urethra and be moved over the mucosa for a distance of 5 mm. Finally the swab was drawn back into the 2.5 mm tube and the tips of the cottonwool swabs were immediately rubbed over the surface of blood agar plates and MacConkey agar plates. All of the plates were incubated at 37°C for 24 h and then examined.

Results

See Figure 2.

Discussion

This study has shown that the prevalence of significant quantities (if defined as greater than 5

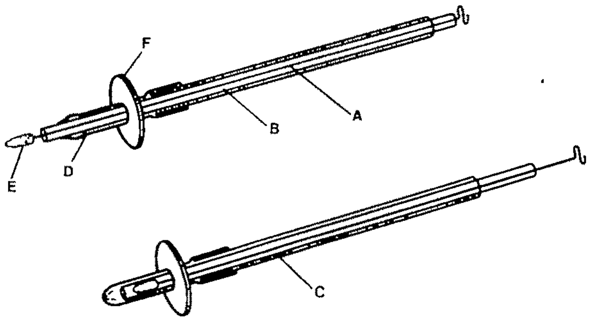

Fig. 1 Swab introducer. A: fine metal rod. B: 2.5 mm plastic tube. C: 3.5 mm plastic tube D: rubber diaphragm. E: cottonwool swab. F: washer at 1.3 mm.

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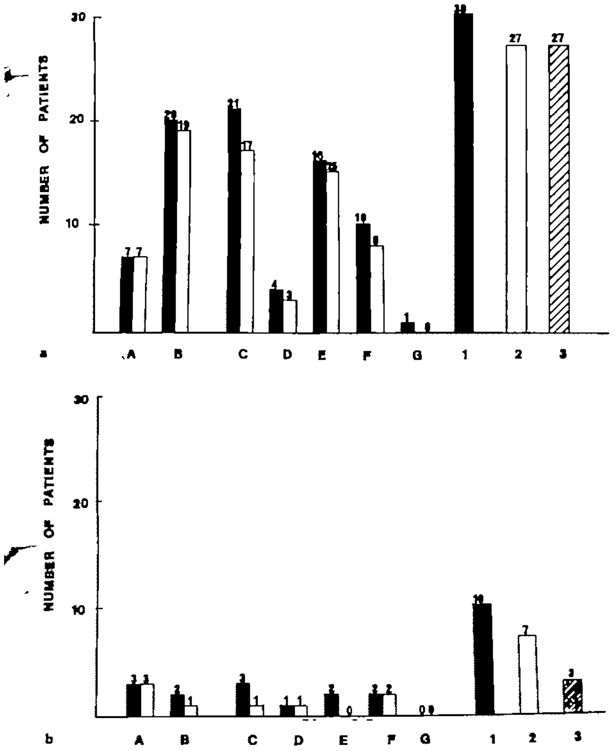

Fig. 2
(a) Meatus
(b) 1.5 to 2 cm proximal to the meatus

■ Number of patients with organisms cultured.
□ Number of patients with 5 colonies of organisms cultured.
▨ Number of patients with significant (5 colonies) quantities of potential pathogens.

Organisms

A. Lactobacilli B. Diphtheroids	}	Potential pathogens
C. Micrococci D. Staphylococci E. Enterococci F. *Esch. coli* G. *Proteus*	}	Pathogens

1. Total number of patients with organisms cultured.
2. Total number of patients with 5 colonies cultured.
3. Total number of patients with 5 colonies of potential pathogens cultured.

colonies) of potential pathogens is 90% at the urethral meatus and only 10% at a point just proximal to the midurethral high pressure zone (1.5-2 cm from the meatus). It would appear that with this new method of study, support can be given to the hypothesis of Mayo and Hinman (1973) who have suggested "that the static midurethral high pressure zone acts as a relative barrier to bacterial ascent".

Additional factors which may reduce the bacterial content of the upper urethra include intrinsic mucosal activity, mucus production and possibly antibacterial secretions (Hutch, 1970). Hutch has suggested that the paraurethral glands may by their mucus production slow down or prevent the ascent of bacteria into the bladder. Although noone has convincingly been able to demonstrate antibacterial activity from the mucus of the paraurethral glands (Hutch, 1970), it should be remembered that these glands in the female are represented by the prostate in the male. Stamey *et al.* (1971) have shown that the prostate gland in the dog produced a fluid with antibacterial activity. Future studies may define antibacterial activity in the urethral mucus or perineal secretions.

These results contrast with the well established work of Cox (1966), who reported that 81% of the normal female population had bacteria 2 to 3 cm proximal to the meatus.

Mortimer *et al.* (1967) cultured bacteria in 49% of their patients at a point 2.5 cm proximal to the meatus. In the present study only 33% of the patients had organisms cultured from the proximal urethra 1.5 to 2 cm from the meatus: 100% of the swabs from the distal urethra grew organisms.

The instruments used by Cox and Mortimer are illustrated in Figure 3. Cox used an exfoliating rubber cot which was used to map the distribution of organisms along the urethra (Fig. 4).

By pulling on the string, the rubber cot was unfolded back into its containing sheath. The sheath was then removed and the rubber cot

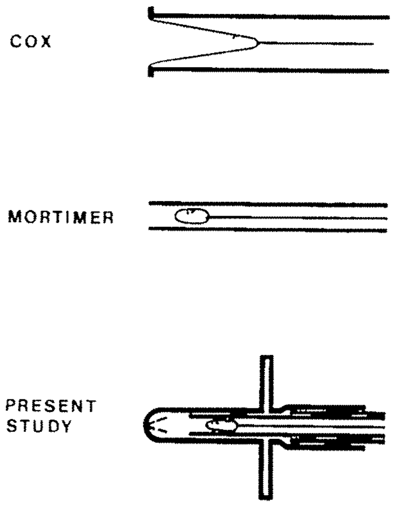

Fig. 3 Methods.

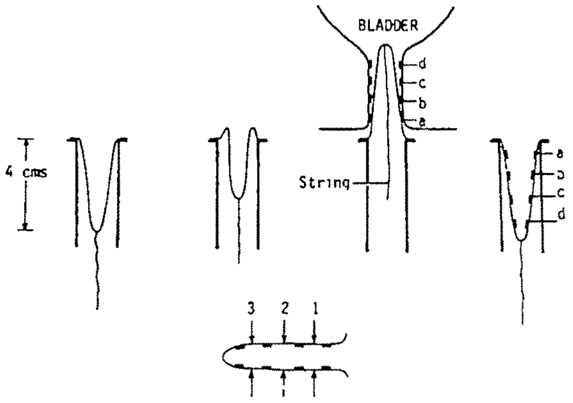

Fig. 4 Cox's instrument.

divided by scissors into 4 equal segments which were cultured. Mortimer used a swab which was contained within an open-ended sheath.

Both methods are open to criticism. Even if the method using the exfoliating rubber cot is effective in mapping the distribution of organisms it suffers from one serious mechanical problem. When the rubber cot is divided into 4 equal segments for culture, the inner surfaces, together with a layer of organisms and fluid, are pushed together. This results in organisms being milked up and down the inside of the rubber cot. Therefore the segments representing the proximal urethra may be contaminated by the organisms that have been milked along the rubber cot each time it is divided. The technique with the open-ended sheath is associated with a risk of organisms collecting within the sheath as it moves along the distal urethra. These organisms will then be transferred to the swab as it is pushed through the sheath.

The difference in results in the reported series is related to variations in technique for studying the urethral flora. It is hoped that with the current method of study, the risk of contaminating the swab with organisms from the distal urethra is reduced to a minimum.

The urethra proximal to the midurethral high pressure zone contains few, if any, potential pathogens in the majority of patients. The fluid which collects distal to the high pressure zone acts as a reservoir for infection and has significant quantities of potential pathogens in 90% of patients.

Hence the high pressure zone acts as a relative barrier to bacterial ascent and together with urethral washout and intrinsic mucosal activity forms part of the urethral defence mechanisms against urinary tract infections.

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Clitoroplasty in Intersex: a New Technique

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Summary—A new technique of reduction clitoroplasty is presented. The procedure consists of a subtotal resection of the shaft of the clitoris with preservation of the dorsal neurovascular bundle of the glans. The purpose is to preserve erogenous glans clitoris and the erection of the crura.

The anatomical results in 8 patients were excellent; partial necrosis occurred in a 12-year-old patient. The functional result remains unknown since the children are still young.

This technique of clitoroplasty is, as far as we know, the most conservative procedure to date.

In feminising the external genitalia in cases of intersex, clitoroplasty should aim to establish a result that is as close as possible to the normal female clitoris, while sparing the sensitivity and the erectile function of this organ. The technique proposed appears to meet all of these conditions.

Method

The glans penis is drawn forward. A wedge incision started on the dorsum of the glans is extended ventrally on either side of the frenulum (Fig. 1). The anterior portion of the incision passes just behind the corona and spares the hood. Its posterior portion is on the base of the shaft. It is extended ventrally to the medial aspect of the labia majora. In removing the skin, great care should be taken to spare the subcutaneous tissue which contains the dorsal neurovascular pedicle (Fig. 2). The latter is isolated and protected because it supplies blood to the glans (Fig. 3). Dissection of the pedicle may be difficult: theoretically it is started at the junction of the crura, and as much subcutaneous fat as possible is preserved around the vessels (Fig. 4). Subsequently, the corpora cavernosa are freed for the entire length of the shaft, while keeping the dissection on Buck's fascia. This latter portion of the dissection is not difficult, but great care should be taken on the ventral aspect to avoid injuring the frenulum and inferior vessels (Fig. 4). The crura are then dissected up to their pubic attachments. This

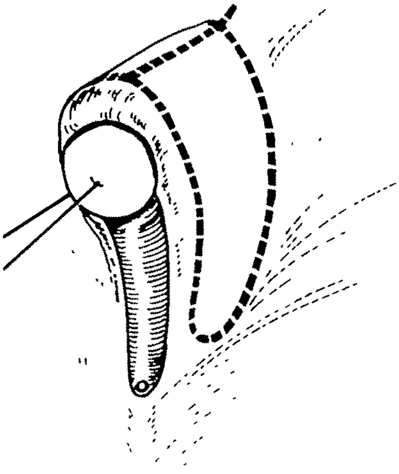

Fig. 1 The wedge incision.

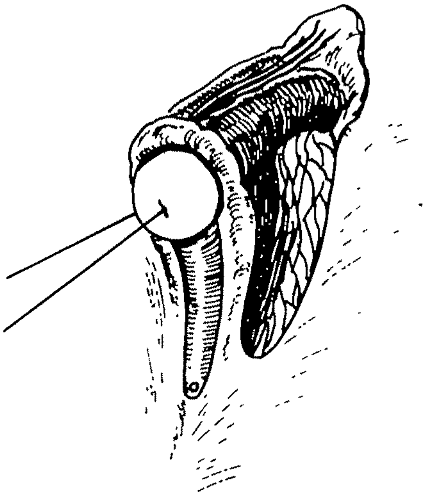

Fig. 2 The skin is excised, avoiding the dorsal pedicle.

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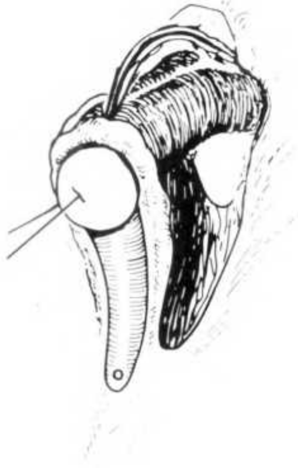

Fig. 3 The corpora cavernosa are completely dissected. The dorsal pedicle and the frenulum attachments are preserved.

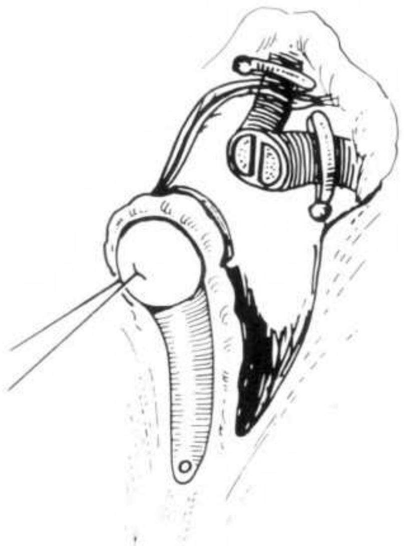

Fig. 5 The crura are clamped and the corpora cavernosa are resected.

will permit their clamping with vascular clamps (Fig. 5). The entire fused portion of the corpora cavernosa is then resected, leaving only a few millimetres behind the glans and at the origin of the shaft. These 2 surfaces are then approximated with 6/0 polyglycolic acid stitches. Only Buck's fascia is sutured with numerous stitches (Fig. 6). Clamps are then removed and haemostasis is checked. Usually it is satisfactory. Sometimes it is necessary to add a few more stitches.

The clitoris now has both a normal length and position. Blood supply and erectile function of the crura have not been disturbed. The glans remains vascularised by the dorsal vascular pedicle and by the frenular attachments as demonstrated by Spence and Allen (1973), Kumar *et al.* (1974) and Shaw (1977). The distal portion of the corpora cavernosa may be left with a poor blood supply and a poor erectile function, but these are not real problems for the following reasons:

1. This is more or less the normal state in the female (Testut, 1931).
2. It causes the spontaneous shrinkage of the

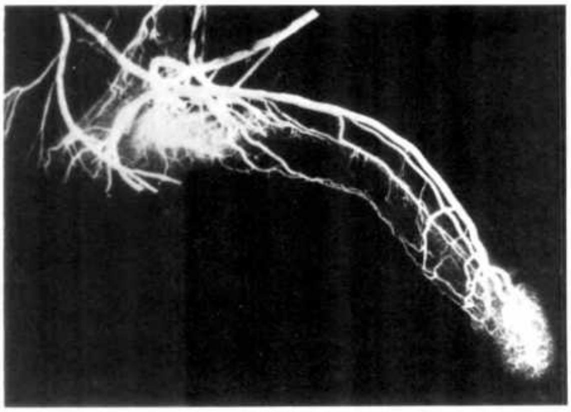

Fig. 4 Post mortem arteriography showing clearly the dorsal pedicle.

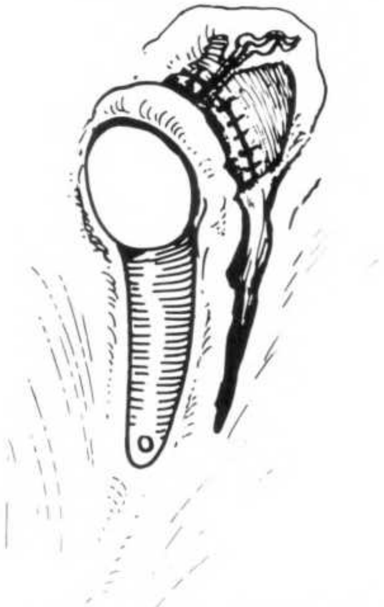

Fig. 6 Approximation with fine suture, taking Buck's fascia only.

glans which we, like Spence and Allen (1973), have observed. This is very advantageous from the cosmetic point of view and it avoids the necessity of performing subsequent wedge resection of the glans, which is often necessary with Pellerin's technique (Pellerin, 1965).

3. In view of the feasibility of penis reimplantation, one might consider it possible for the distal portion of the corpora cavernosa to regain some blood supply (Schulman, 1973; Engelman *et al.*, 1974). X-ray study by opacification of the corpora cavernosa would seem advisable.

Results

This technique has been carried out in 9 children; all except one aged 12 were between 12 and 24 months old. Vaginoplasty was performed at the same time. The cosmetic result was excellent. The clitoris shaft obtained a normal length. The glans volume shrank enough to make any complementary resection unnecessary.

In one case the result was not perfect: the glans became very blue and we observed a subtotal necrosis. This was in a 12-year-old patient in whom the dissection of the dorsal pedicle was very difficult and who had had a circumcision in the neonatal period.

The only remaining problem seems to be a relatively highly placed clitoris.

It is too early to evaluate the functional results, all of our patients being still very young.

Discussion

Unlike Hamilton and Dennison (1967), we consider, as do other authors (Spence and Allen, 1973; Engelman *et al.*, 1974) that clitoris hypertrophy is permanent and does not regress with hormonal treatment. The need for surgery seems obvious. Although total amputation of the clitoris is a simple and quick method, it is a mutilating one and therefore no longer performed. Even if satisfactory sexual activity appears to remain possible (Money *et al.*, 1955) clitorectomy is disadvantageous since it probably hampers sexual learning.

Clitoroplasty by recession (Ombredane, 1939; Kaplan, 1967) is insufficient and no longer performed.

Clitoroplasty by recession and relocation of the corpora cavernosa plicated and fixed to the inferior aspect of the pubic arch, as described by Pellerin (1965), was an important step forward. Nevertheless, it is a time-consuming and difficult procedure because of the length and volume of erectile tissue to be hidden. In addition it is often necessary to perform a subsequent wedge resection of the glans. Finally, the erectile capacity of the corpora cavernosa appears to be sacrificed with this method because of the plication.

The new technique proposed appears to be more satisfactory than those previously used because the hypertrophied portion of the clitoris is removed and a normal morphological aspect is achieved.

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Priapism—Conservative Treatment Versus Surgical Procedures

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Summary—Fourteen patients with priapism have been treated over the last 12 years. Two patients had a recurrence 2 and 5 years after the primary incident. Abuse of alcohol (often combined with psychotropic drugs) and the use of antihypertensive drugs were the most prominent aetiological factors. Three out of 9 patients treated conservatively and 5 out of 6 patients treated with a shunt procedure have preserved their erection ability.

Our results indicate that conservative treatment is not justified and that a shunt procedure should be performed with the least possible delay.

Priapism is a rare complaint defined as a prolonged and painful erection of the corpora cavernosa without sexual desire. The exact mechanism is unknown and in many subjects the cause is idiopathic, but there are several well known aetiological factors (Table 1).

When priapism was described in 1824 by Callaway, treatment included cold lotions, calomel, venesection and the application of leeches.

The modern treatment of priapism until the past decade has been mainly conservative, involving the use of trimetaphan, ketamine, fibrinolysin, heparin, oestrogen, sedatives and dextran. Hyperbaric oxygen, nerve blocks at different levels and general anaesthesia have also been used (Abeshouse and Tankin, 1950; Hinman, 1960; Rubin, 1968). The variety of treatments reflects the lack of understanding of the causes of priapism. The criteria for successful treatment are (1) that the circulation of the corpora cavernosa is restored, (2) that the priapism is relieved and (3) that the patient later has a normal penile erection. Experience has shown that protracted priapism nearly always leads to fibrosis of the corpora cavernosa and impotence.

Since the first results of surgically established cavernosaphenous and cavernospongiosus shunting were published (Grayhack *et al.*, 1964; Quackels, 1964), many other reports of the varying success of these procedures have appeared (Johansson and Lindqvist, 1970; Klein *et al.*, 1972; Reid and Homsy, 1972; Sacher *et al.*, 1972; Wellwood *et al.*, 1972; Lehtonen and Tenhunen, 1973; Medeiros and Carvalho, 1973; Carter *et al.*, 1976). Apart from these 2 shunt operations, descriptions of other procedures have also been published: anastomosis between one corpus cavernosum and glans of the penis (Ebbehoj, 1975; Tarasuk and Schneider, 1976) and anastomosis of the corpus cavernosum to the dorsal vein of the penis (Barry, 1976). A new non-surgical procedure to treat priapism has also been reported (Wear *et al.*, 1977). By inserting angiographic catheters the pudendal arteries were occluded by infusion of an autologous clot. In the only published case the primary result was excellent and erection ability was preserved.

Patients (Table 2)

Since 1966, 14 patients with a mean age of 39 years (range 25-55 years) have been treated for priapism on 15 occasions. Nine patients were alcoholics and 4 of these were being treated with

Table 1 Aetiology of Priapism

Abuse of alcohol
Antihypertensive drugs
Psychotropic drugs
Trauma
Metabolic disorders
Psychosis
Sickle cell anaemia
Malignancy
Anticoagulant therapy
Rabies

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Table 2

Age	*Predisposing factors*	*Treatment*	*Post treatment*	
			Erection	*Orgasm*
F R 55	Antihypertensive therapy	Conservative	†	*
S-Å.B 26	Alcoholic	Conservative	‡	*
H.D 34	Alcoholic	Conservative	§	§
A.S 53	Antihypertensive therapy	Conservative	§	§
K.G 36	Alcohol, psychotropic drugs	Conservative	*	*
A J 53	Alcoholic	Conservative	§	§
K S. 46	Alcohol, psychotropic drugs	Conservative	‡	‡
K.O 39	Alcoholic } same patient	Conservative	*	*
K.O 41	Alcoholic	Cavernospongiosus shunts bilat	*	*
H A 33	Psychosis, psychotropic drugs Anticoagulant therapy	Conservative	‡	‡
A.O. 31	Alcoholic, psychotropic drugs	Cavernospongiosus shunts bilat	†	*
J.I. 41	Alcoholic	Cavernospongiosus shunts bilat* Cavernoglandular shunts bilat	†	*
S-A P 24	Temporary alcohol abuse	Cavernosaphenous shunt	*	*
H.D 42	Alcoholic, psychotropic drugs	Shunt between c. cavernosum and dorsal vein of penis* Cavernospongiosus shunt	‡	‡
B.A 25	Crohn's disease, parenteral feeding	Cavernosaphenous shunt* Cavernoglandular shunts bilat	†	*

* Normal function. † Reduced function ‡ No function § No information.
The fistula of patient B.A. 25 has been closed The patient is functioning well and has recently fathered a child.

psychotropic drugs. Two patients were on antihypertensive drug therapy, one on Ismelin (Ciba) and the other on Ismelin combined with Apresoline (Ciba). One psychotic patient had had both psychotropic and anticoagulant therapy after a thrombosis. One young man developed priapism after temporary alcohol abuse. Another suffered from Crohn's disease and developed priapism during protracted parenteral feeding. Except for 1 patient (H.D. 42) whose admission to hospital was delayed for 3 days, all patients were treated within one or 2 days following the onset of priapism. Until 1974 our approach was conservative and treatment consisted of puncture of the corpora cavernosa and administration of oestrogens, sedatives, anticoagulants and anticholinergic drugs. Epidural block was tried in one case.

Since 1974 treatment has been surgical and 6 patients have had shunts of different kinds. Four patients had cavernospongiosus shunts, 3 of which were bilateral, and 2 had unilateral cavernosaphenous shunts. In the case of one patient with an unsuccessful anastomosis between the corpus cavernosum and the dorsal vein of the penis, we proceeded immediately to bilateral cavernospongiosus shunts. In 2 cases where the function of the primary shunts was in doubt, cavernoglandular shunts were performed the following day.

Two patients were treated for priapism on 2 separate occasions. One of them (K.O. 39) was treated conservatively the first time, but when he was admitted again 2 years later, bilateral cavernospongiosus shunts were made. The other (J.I. 41) had been operated upon 5 years earlier at another Swedish hospital with simultaneous bilateral cavernosaphenous shunts and he also received cavernospongiosus shunts on the second occasion.

Operative Procedures

All operations were performed under general anaesthesia with the patient in the lithotomy position, and all but one patient had a suprapubic cystostomy. The creation of a cavernospongiosus shunt commenced with an incision in the anterior perineum. The bulbocavernosus muscle was split in the midline and the corpora cavernosa and spongiosa dissected free for 3 to 4 cm. Thereafter one of the corpora cavernosa was punctured and irrigated with heparinised saline. A fenestration 4 × 10 mm was made laterally in the corpus spongiosum and medially in the corpus cavernosum. The anastomosis was then sutured with continous non-absorbable material, as in all shunts of this kind.

When a cavernosaphenous shunt was chosen, the saphenous vein was first dissected free through 2 small incisions on the thigh for at least 12 cm measured from the fossa ovalis. After perineal incision and dissection of the corpus cavernosum, the vein was cut distally and brought through a subcutaneous tunnel and an end-to-side anastomosis was established. In one of our patients an anastomosis was created with an end-to-side technique between the dorsal vein of the penis and one of the corpora cavernosa. Cavernoglandular shunts were performed with deep scalpel incisions through the glans penis into the underlying corpora cavernosa on each side of the urethra. The corpora cavernosa were irrigated with heparinised saline and then the incisions of the glans were sutured.

Results

Eleven of the original 14 patients are alive and have been interviewed (Table 2). Three patients (F.R. 55, A.S. 53, A.J. 53), all conservatively treated, have died, one from alcohol intoxication and 2 from heart failure. Another, treated conservatively (H.D. 34), refused to co-operate in the follow-up.

Two of the 9 patients treated conservatively preserved their erection ability and one of them has since fathered a child. One of the patients who died from heart failure (F.R. 55) reported at an early follow-up that he had impaired erection but normal orgasm. Another non-surgically treated patient (S-Å.B. 26) reported unchanged orgasm but loss of erection.

Five of the 6 patients treated with a shunt have erections but 3 of them describe the erection as "not as good as before". They can take part in sexual intercourse and orgasm is unchanged. One of them has also fathered a child since the shunt procedure. The sixth patient (H.D. 42) has no erection.

Three of the patients treated with a shunt have attended our out-patient department for further examination. One of them had received bilateral cavernospongiosus shunts and the other a unilateral cavernosaphenous shunt. Both are functioning well (A.O. 31, S-Å.P. 24). The third patient (B.A. 25)—suffering from Crohn's disease—developed a post-operative haematoma following a unilateral cavernosaphenous shunt procedure and next day he was treated with cavernoglandular shunts. He has difficulty in gaining an erection but is still able to have intercourse with his wife. Cavernosography has revealed that the shunts are still open and closure is planned. Physical examination and laboratory data, including hormone analyses, are normal in these 3 men. To evaluate their penile arterial circulation a Doppler technique has been used. Systolic penile blood pressure has been measured and compared with systolic brachial pressure. The acceleration of flow-velocity in the penile arteries measured by a Doppler probe and registered on a polygraph has been compared with the flow-velocity in the brachial artery and the ratio between these—the penile acceleration ratio (PAR)—has been calculated. Their penile systolic blood pressure was about the same as their systolic arm blood pressure and the PAR values in their best penile artery were normal at 0.44, 0.66 and 0.43 respectively (Olsson *et al.*, 1978).

Discussion

During the last 15 years the treatment of priapism has changed from a conservative approach to an active surgical procedure with the creation of venous shunts. The results of the more active treatment have been promising in our experience as well as in that of several others (Klein *et al.*, 1972; Nair, 1976; Kihl *et al.*, 1978). Two factors seem to be especially important for a good result:

1. minimum delay from the onset of priapism until operation, and
2. quick detumescence following the operative procedure.

Since priapism can recur after successful treatment, we recommend unilateral shunting, which makes it possible to use the same technique on the opposite side if necessary.

There are, however, those who advocate a bilateral procedure (Medeiros and Carvalho, 1973; Nair, 1976). Erection ability often returns some weeks after a successful operation. Fibrosis of the corpora cavernosa was seen in patients whose treatment was delayed. This change can be clinically evaluated by palpation as a tough induration of the corpora cavernosa. Among our 14 patients, abuse of alcohol and treatment with drugs seemed to be the dominating factors. A similarly high incidence of alcoholism has been reported in another Swedish investigation (Kihl *et al.*, 1978). It is interesting that none of our patients had haematological disease or trauma as possible aetiological factors, as described elsewhere (Rosenberg, 1971; Goulding, 1976; Oppenheimer, 1976; Pershy and Kursh, 1977; Wear *et al.*, 1977; Baron and Leiter, 1978). In some studies the majority of patients had no known aetiological factors (Nelson and Winter, 1977), while others reported that sedatives provoked priapism (Schmidt, 1971;

Appell *et al.*, 1977). These findings are not in accordance with our experience. We have not seen priapism in any patients either with rabies or malignancy (Abeshouse and Tankin, 1950; Narayana *et al.*, 1977; Talaulicar, 1977).

Our results following shunt procedures have been satisfactory, except for the patient (H.D. 42) whose operation was delayed for more than 72 h and another (B.A. 25) who had an open cavernoglandular shunt. The result of shunting to the dorsal penile vein in our single case was inefficient, probably because of the combination of a small vessel and the high viscosity of blood in the corpora cavernosa. All other methods for venous shunting seem suitable, but some of them carry certain risks. A fistula into the urethra has been described after a cavernospongiosus shunt (Sacher *et al.*, 1972). The cavernoglandular shunt sometimes leaves a permanent venous opening between corpora cavernosa and glans, leading to diminished or absent erection; this is well illustrated by one of our patients (B.A. 25). Operative closure of the shunt may be required (Ebbehoj, 1975).

It is concluded that, regardless of aetiology, priapism is a condition that demands surgical treatment in the form of an urgent shunt operation.

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Surgical Correction of Torsion of the Penis

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Summary—Torsion of the penis is a rare anomaly, believed to be due to abnormal skin attachment and not to any structural abnormality of the corpora. The rotation is usually to the left in a counter-clockwise fashion. The urethral meatus is placed in an oblique position and the median raphe makes a spiral curve from the base of the penis towards the meatus.

Three boys with congenital torsion of the penis are reported. A corrective operation for this condition is described.

Penile torsion was first described by Verneuil in 1857, but in the past no operative correction was recommended, since attempts to move the skin around were believed not to correct the spiral alignment of the corpora cavernosa.

Patients

Patient 1 A 5-year-old was referred because of a twist of the penis to the left; there were no urinary symptoms. Examination showed a 90° torsion with a normal meatal orifice.

Patient 2 A 10-year-old was referred because the urine stream sprayed to the left when he micturated. Examination revealed a 90° torsion; the meatus was terminal and adequate (Fig. 1).

Patient 3 A 6-year-old presented because of spraying on micturition and he had some difficulty on passing urine. Examination revealed a 90° torsion, a minor degree of glandular hypospadias and a narrow meatal opening (Fig. 2).

Operative Procedure

In patient 1, the torsion was corrected by making a circular incision at the base of the penis and then dividing the tissues all around, down to the corpora; de-rotation was established and the skin was sutured in a slightly over-corrected position (Fig. 3).

In patients 2 and 3, the foreskin was excised, as in a routine circumcision operation. The sleeve of penile skin was dissected and pushed back as far as the root of the penis. Thick fibrous bands were seen extending from the base of the penis, across the shaft in a spiral fashion towards the base of the glans, and were the cause of the twist. After division of these bands near their basal attachment, spontaneous de-rotation occurred. The skin was pulled forwards and sutured around the coronal sulcus in a slightly over-corrected position.

Results

Correction of the torsion was complete with satisfactory cosmetic appearances. Patient 1 developed

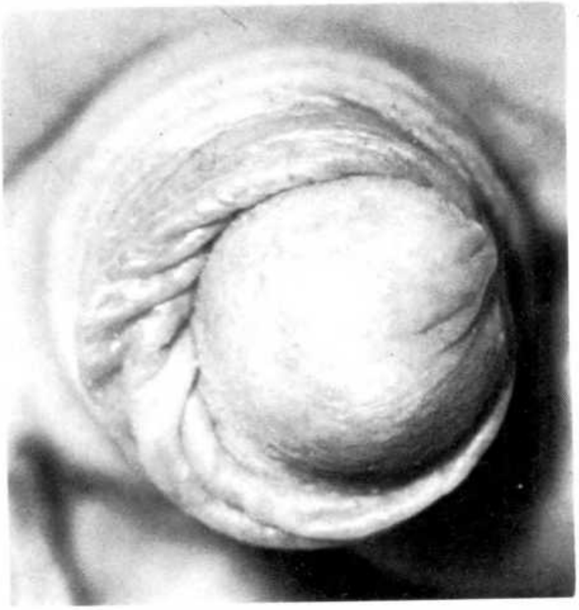

Fig. 1 Penile torsion with normal meatus.

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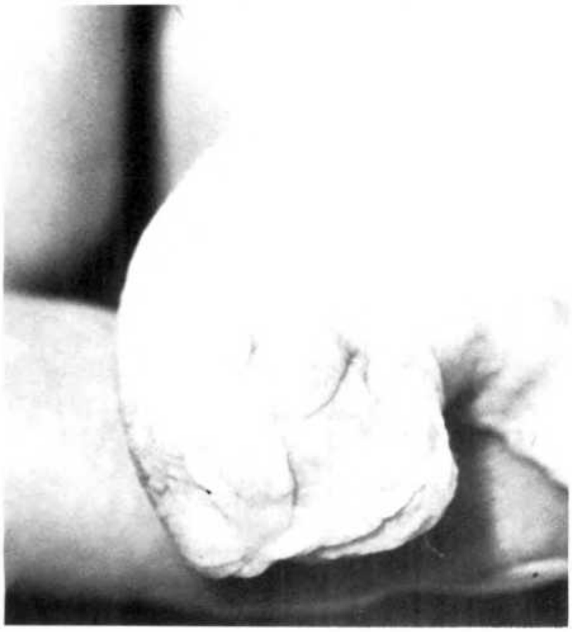

Fig. 2 Penile torsion with minor degree of hypospadias.

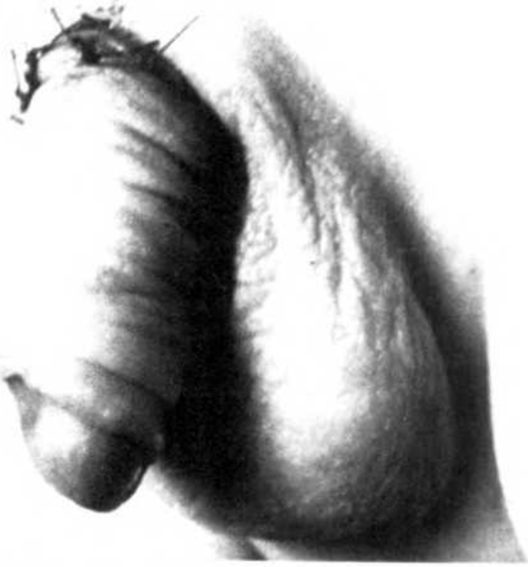

Fig. 3 Post-operative result in patient 1.

a slightly hypertrophic scar at the root of the penis.

Discussion

Surgical correction of torsion of the penis was described by Fèvre in 1947; he established a successful reversal of torsion by removing the crura from the pubis and reinserting them in a normal position.

Johnston (1977) described a corrective procedure, which was performed in our first patient. The technique employed in patients 2 and 3 has 2 advantages—no devascularisation of the skin and it avoids leaving a circular scar near the pubis which may develop keloid.

This procedure is suitable for patients with a normally situated meatus and in cases with a minor degree of hypospadias which do not require the use of the foreskin for subsequent repair.

Johnston's technique is recommended in patients with a severe degree of hypospadias, and the hypospadias repair should be deferred for 6 months after correction of the torsion.

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Limitations of the Doppler Flow Meter in the Diagnosis of the "Acute Scrotum" in Boys

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Summary—Doppler examination of the "acute scrotum" was performed in 37 boys. The results of these examinations were consistent with the findings at operation in all but 4 boys. Of the latter, 3 were amongst the group of 11 with torsion of the spermatic cord, and the other was an infant with an irreducible inguinal hernia. At present, the results of ultrasound examination of blood flow are unreliable in the diagnosis of acute scrotal pathology in boys. This lack of reliability is particularly noticeable when symptoms have been present for more than 24 h.

In 1974, Milleret and Liaras described the use of the ultrasound stethoscope in the diagnosis of 2 cases of torsion of the testicle. Six months later, Levy (1975) reported his findings in 7 cases of "acute scrotum". In all 3 patients with torsion there was decreased blood flow through the affected testis, whereas increased flow was noted in 2 patients with epididymitis. Shortly afterwards, Pedersen *et al.* (1975) used the Doppler principle to examine 45 patients. A neonate and 4 adults had torsion of the cord and all 5 were correctly diagnosed. With these reports in mind, it was decided to evaluate the accuracy of the ultrasound flow meter in a series of boys.

The probe of the flow meter contains a quartz crystal which transmits ultrasound waves into the tissues which in their turn reflect the waves back to the probe to be received by another quartz crystal. Corpuscular fluid, such as blood, and vessels containing fluid with variable rates of flow, as is the case in most blood vessels, will cause a distortion of the reflected beam according to the Doppler principle. The apparatus contains sophisticated electronic circuits which convert the reflected ultrasound waves into an audible signal, the intensity of which is proportional to the magnitude of blood flow in the underlying vessel. Hence, in the case of torsion of the spermatic cord, it would be expected that there would be no audible signal from the flow meter, a so-called positive test, whereas with a negative test a signal indicating normal blood flow should be heard.

Patients and Methods

Between July 1978 and August 1979, 37 consecutive boys with an acute scrotal problem were studied prior to operation with an ultrasound flow meter using the methods described by Levy (1975) and Pedersen *et al.* (1975). However, in those boys with exquisite tenderness it was thought to be unjustified and unethical to compress the scrotum between the testis and the probe because this would have caused undue suffering. Thereby an element of error may have been introduced, since the circulation through the layers of an oedematous scrotum may have been detected by the flow meter. A transducer operating nominally at 10 mHz (9.7) was used with the battery operated Doppler flow meter (Parks Electronics Laboratory, Model 812, Beaverton, Oregon, USA).

Results

The ages of the patients can be seen in Figure 1;

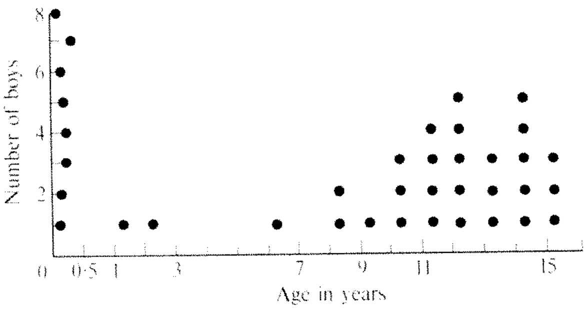

Fig. 1 The ages of the 37 boys at presentation.

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Table 1 Results of Ultrasound Tests and Final Diagnoses

Final diagnosis	*Pre-operative diagnosis correct*			*Pre-operative diagnosis incorrect*		
	Increased flow	*Normal flow*	*Decreased flow*	*Increased flow*	*Normal flow*	*Decreased flow*
Irreducible inguinal hernia	1	6		1		
Reducible hernia	1					
Traumatic swelling or haematoma		2				
Idiopathic scrotal oedema		1				
Torsion of hydatid of Morgagni	7	2				
Acute hydrocele			1			
Torsion of testis			6	1	4	
Abscess	1					
Idiopathic oedema of the cord				1	1	1
Total	10	11	7	3	5	1

7 of the boys were less than 2 months old. The final diagnoses can be seen in Table 1.

The testis and cord were studied in 8 cases of irreducible inguinal hernia. In 6 of these the blood flow was judged to be normal on ultrasound examination and all 6 testicles seemed to be normal at operation. Increased flow was detected in an infant aged 2 months and a viable, but blue and congested testis was found. Increased flow was found in a 9-week-old boy with a 2-day history of scrotal swelling, but at operation a necrotic testis was found distal to an incarcerated Richter's hernia.

Normal flow was detected in 2 boys with minor trauma to the testis and in both testicles of a boy with idiopathic oedema affecting both sides of the scrotum. Blood flow seemed to be decreased in a boy with an acute hydrocele, although it is probable that the intensity of the reflected ultrasound was simply decreased by the relatively large amount of fluid between the probe and the testicular blood vessels.

Of the 9 boys with torsion of the hydatid of Morgagni, the flow was increased in 7 (6 of whom presented after a delay of over 24 h from the time of onset) and normal in 2. Of the latter, one presented within 12 h of onset, whereas the other delayed attention for 2 days. Torsion of the spermatic cord had occurred in 11 boys and flow was absent in 6, all of whom had a necrotic testis. A boy with a torsion of 2 days' duration was thought to have increased testicular blood flow, but exploration revealed a twisted, necrotic testis. Of the 4 boys with torsion and apparently normal blood flow, 2 had a necrotic testis and 2 had a twisted but viable gonad. One of the latter, who had had symptoms for 6 days, was diagnosed as a case of torsion on clinical grounds because the organ was enlarged and craggy, although the possibility of torsion of a neoplastic testis had been considered. The other boy with apparently normal flow had had symptoms for 12 h; since he had had similar attacks in the past, he was diagnosed as suffering from a recurrent, spontaneously correcting torsion of the left spermatic cord. However, at operation a loose twist through 180° of a left "bell clapper" testis was found. The blood supply had not been compromised and the testis was viable. After incising the other side of the scrotum to perform right orchiopexy, the surgeon was surprised to find a torsion through 180° of a viable right "bell clapper" testis. There had never been symptoms arising from the right side of the scrotum.

Recently, the flow meter was used to investigate the swelling of the left testis of a neonate of 1.8 kg. The boy, one of twins, was seen at the age of 11 h, and there was very little scrotal oedema. His heart rate was about 160 beats per min. No flow could be heard to the affected testis, although the digital pulse of the examiner, at about 70 beats per min, could he heard. At operation an infarcted testis was found, the result of a typical neonatal supravaginal torsion of the cord. Presumably the liquefied testis had acted as a blob of trans-sonic jelly, and this "sign" may be of some significance in the examination of the tiny testes of small infants.

Symptoms suggestive of torsion of the cord occurred in 3 boys; 2 of these were suspected of having undescended testes, the gonads being in the groin at the time of presentation. Blood flow was increased in one, normal in another, and reduced in the third. The findings at operation

Table 2 The Results of the Ultrasound Examination Correlated with the Duration of Symptoms. The 3 Cases of "Idiopathic Oedema of the Cord" Have Been Omitted

	Correct interpretation of ultrasound examination	*Misleading findings on ultrasound examination*
Symptoms present for less than 24 h	17	2
Symptoms present for over 24 h	10	5

were similar in all 3; the retractile, viable testis was lying in the superficial inguinal pouch; there was oedema of the cord, but not of the scrotum or gonad, and there was a small amount of fluid, in excess of normal, in the tunica vaginalis. In no case was there any evidence of torsion nor of any abnormality that would predispose to torsion. There was no obvious epididymitis and bacteriological cultures of the urine and fluid from the tunica were sterile. These have been labelled cases of "idiopathic oedema of the cord".

Table 2 demonstrates the results of the flow studies in boys who had symptoms for more or less than 24 h. In the latter, the test could have been misinterpreted in 2 cases—the boy with the acute hydrocele and the boy with normal flow who was found to have 2 viable testes despite the unexpected discovery of bilateral torsions. In the 15 who had symptoms for more than a day, the test was definitely misleading in 4 cases. One of these was the infant with increased flow in whom there was a necrotic testis caused by an incarcerated Richter's hernia. The other 2 had apparently normal flow despite the fact that each possessed a necrotic testis, twisted for 2 to 3 days (Fig. 2). A boy with a 2-day history seemed to have increased flow but was also found to have an infarcted organ. A fifth boy, who had had symptoms for 6 days, had normal blood flow: at surgery the testis was viable but a torsion of the cord was present.

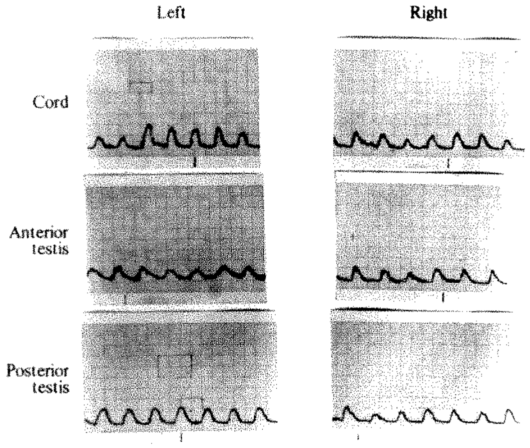

Fig. 2 Recording of the blood flow in a case of right testicular necrosis due to torsion of 2 days' duration.

Discussion

In discussing the value of ultrasound examination of the scrotum, Levy (1975) stated that the distinguishing feature of torsion of the testis was loss of blood flow and that the Doppler stethoscope could accurately demonstrate the presence or absence of flow. Thompson *et al.* (1975) failed to detect blood flow in any of their 7 patients with torsion of the cord. Initially, Perri *et al.* (1976a) reported likewise, but later described the case of a boy of 12 years with a 5-day history of scrotal pain and swelling in whom increased flow was found on Doppler ultrasound examination. Testicular scanning with technetium-99m indicated an ischaemic testis and a gangrenous gonad was found at operation (Perri *et al.*, 1976b). In 1977 Nasrallah *et al.* reported 4 false negative Doppler examinations in cases of torsion, all confirmed by surgical exploration, and they warned against undue reliance on the test in the diagnosis of this condition. Their patients were examined between 16 and 72 h after the onset of pain. The results of the present series support the conclusions of Nasrallah *et al.*

It is important to note that ultrasound examination will be especially misleading in those cases of torsion where there is persistent blood flow. By and large, these are the cases which will benefit most from early operative correction, and on no account should the unexpected result of a Doppler test militate against early exploration when the clinical findings suggest the possibility of a torsion. In particular, the Doppler test is likely to be very confusing in the case of recurrent, spontaneously correcting torsion. However, in this situation, armed with the information that blood flow seems to be present, the surgeon may be prepared to delay operation for a few hours to allow sufficient time for thorough preparation and premedication of the patient.

It is postulated that in the more usual type of torsion, with several tight twists in the cord, there may be a brief period of intense venous congestion before arterial inflow ceases, and Doppler testing could give the impression of increased vascularity, as suggested by Pedersen *et al.* (1975). Most cases will have passed beyond this phase by the time of arrival at hospital and no flow will be heard in the infarcting organ. After the passage of several hours, perhaps 48 to 72, the scrotum becomes hyperaemic and flow may seem to be restored to normal. With the passage of time, as the inflammatory response increases and the scrotum becomes more hyperaemic, detectable flow to the testis may seem to increase also. Eventually, as the testis atrophies, flow may well return to normal yet again prior to disappearing altogether. In this series no flow was heard in any of the 5 severely ischaemic testes seen between 2½ and 12 h after onset, whereas normal or increased flow was heard in the 3 presenting 2 to 3 days later.

This apparent paradox does not mean that Doppler testing of cases of acute scrotal pathology is without value, and in cases of torsion it is gratifying to be able to hear the return of flow after detorsion (Perri *et al.*, 1978). However, the return of blood supply does not necessarily mean that any long-lasting benefit has been achieved, for spermatogenesis is probably destroyed by total ischaemia lasting for 4 h (Smith, 1955).

Most of the authors referred to above mentioned the finding of increased flow in their patients with acute epididymitis. Presumably this would be the case in boys also, but in this country the incidence of epididymitis before puberty is so low that doubt should be expressed concerning this diagnosis. No case was seen during the 14 months of this survey, and during the last 11 years only 19 (5.5% of cases of "acute scrotum") boys have been treated at this hospital for proven acute bacterial epididymitis (Manley and Brereton, 1980). In this age group the commonest cause of increased flow is torsion of the hydatid of Morgagni. In this condition, normal flow was described by Levy (1975) and increased flow by Perri *et al.* (1976a). Presumably, flow is normal in the initial phases and increased flow develops along with the hyperaemia of the surrounding tissues.

The results of Doppler examination of the 3 cases of "idiopathic oedema of the cord" are of interest, but cannot be explained. In cases of sterile epididymitis Koff (1976) has found evidence to suggest that sudden, brief episodes of reflux of sterile urine along the vas are frequently the cause, but none of the cases in this series has been studied for this phenomenon.

It is suggested that urologists should continue to assess cases of acute scrotal pathology with the Doppler flow meter so that in the future more rational interpretation of the findings will be possible. However, at present, for the average case there can be no better advice than that given by Leape in 1967: when the diagnosis is not immediately apparent, any boy with scrotal pain or swelling should undergo surgical exploration within 4 h. In boys there is no advantage to be gained by delaying surgery until after a testicular scan has been performed because epididymitis and tumours are rare, and in most cases exploration will be recommended sooner or later despite the result of the scan!

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Abnormalities of the Immune System in Patients with Chyluria

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Summary—A study of the immune system in 11 patients with chyluria showed lymphocytopenia, decrease in T cells, a low serum IgA concentration and suppression of delayed hypersensitivity responses to intradermally injected antigens. The similarity of chyluria to intestinal lymphangiectasia and thoracic duct fistula suggests that the immune deficiency may be due to loss of lymph in the urine.

The immune system in patients with chyluria has not been investigated previously, but it is known that they have lymphocyturia (Koo and van Langenberg, 1969; Wiggelinkhuizen *et al.*, 1972) and low peripheral blood lymphocyte counts (Date *et al.*, 1980). In this report we demonstrate some abnormalities of the immune system in patients with chyluria.

Patients and Methods

Eleven unselected patients with filarial chyluria of 4 to 60 months' duration were investigated. None of the patients had microfilaraemia at the time of investigation, but all were from regions endemic for bancroftian filariasis. They had been treated with diethylcarbamazine soon after the onset of their symptoms, either empirically or after demonstration of microfilariae in blood or urine. Other causes of chyluria were excluded. Conditions such as malnutrition, pregnancy, leprosy and parasitaemia, which are known to affect the immune system, were not present and the patients were not on immunosuppressive drugs.

The controls used in this study were age-matched normal subjects from regions endemic for bancroftian filariasis. Patients with non-chyluric filariasis were not used as controls since immunosuppression has been demonstrated in untreated filariasis (Grove and Forbes, 1979). Patients with elephantiasis were also avoided because of possible lymphocyte sequestration in areas of lymphoedema. Cases of non-filarial chyluria were not available for study.

Samples of peripheral blood from patients and controls were taken for total and differential leucocyte counts and quantification of T lymphocytes. T lymphocyte counts were performed by enumerating the spontaneous sheep erythrocyte rosette-forming lymphocytes, after overnight refrigeration, using the method described by Hoffman and Kunkel (1976). Patient samples were run simultaneously with samples from controls. The data were evaluated for statistical difference by the "t" test. Serum immunoglobulins were estimated by the method of Fahey and McKelvey (1965).

The delayed hypersensitivity response was recorded following intradermal injections of 0.02 ml trichophyton antigen (Dermatophytin 1:30; Hollister-Stier Laboratories), 0.1 ml streptokinase-streptodornase (Varidase; Lederle), diluted in 0.9% saline to streptokinase 10 units and streptodornase 2.5 units per ml, and 0.1 ml tuberculin purified protein derivative, equivalent to 1 tuberculin unit (Government of India B.C.G. Vaccine Laboratory, Madras). An indurated area measuring 5 mm or more in diameter for trichophyton and streptokinase-streptodornase and 10 mm or more for tuberculin was classified as a positive reaction. Readings were taken 48 h after injection.

Results

The age and sex of the patients, duration of chyluria and results of laboratory investigations

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Table 1 Clinical and Laboratory Data in 11 Patients with Chyluria

Case number	*Age in years and sex*	*Duration of chyluria (months)*	*Urinary chylomicrons g/l*	*Peripheral blood cell counts × 10^9/l*			*Serum immunoglobulins g/l*		
				Total leucocytes	*Total lymphocytes*	*T lymphocytes*	*IgG*	*IgA*	*IgM*
1	51 F	60	1.3	6.8	0.7	0.6	9.4	1.0	1.1
2	27 F	48	27.0	13.0	0.9	0.5	6.6	0.9	1.6
3	35 F	30	2.5	6.8	2.1	0.7	ND	ND	ND
4	24 M	15	0.4	3.0	0.8	0.5	7.9	1.3	0.6
5	51 F	12	0.6	10.2	1.4	0.6	18.5	1.6	1.7
6	27 F	12	0.5	6.6	0.7	ND	14.5	1.3	1.0
7	46 M	6	2.7	10.2	2.3	0.9	ND	ND	ND
8	35 M	6	9.4	5.0	1.5	1.2	8.5	0.5	0.6
9	22 M	5	0.5	10.1	1.6	0.7	7.5	1.3	0.7
10	32 M	4	0.2	8.8	1.0	0.6	10.5	1.5	0.9
11	24 M	4	0.3	5.6	2.0	1.4	11.6	1.3	1.7
			Normal range:	5.2-10.0*	1.9-4.4*	1.3-3.0*	8.0-17.0†	1.4-4.2†	0.5-1.9†

ND = not done. *Controls. †Normal range for the laboratory

are shown in Table 1. None of the patients had a history of increased susceptibility to infection.

Compared with controls, patients with chyluria showed a highly significant reduction in total lymphocyte ($P<0.001$) and T lymphocyte ($P<0.001$) levels, with no significant difference in total leucocyte counts. T lymphocyte counts were significantly lower in patients who had had chyluria for a year or more, in contrast to those with chyluria of shorter duration ($P<0.05$).

Serum IgG and IgM levels were within the normal range in all but one of the patients studied but IgA levels were lower than normal.

The results of delayed hypersensitivity skin reactions are shown in Table 2. There was a significant reduction in delayed hypersensitivity responses in patients as compared with controls ($P<0.01$, Fisher's exact probability test).

Discussion

Immunosuppression with elevated IgG levels has been reported in bancroftian filariasis (Grove and Forbes, 1979), but it is unlikely that filariasis by itself is the cause of immunosuppression in patients with chyluria. Increased IgG levels were not present in our patients and reduction in T cell counts has not been reported in bancroftian filariasis. All of the patients in this study had been treated with diethylcarbamazine soon after the onset of chyluria—many months before the study. The correlation between the duration of chyluria and reduction in T lymphocyte levels also indicates that chyluria rather than past filarial infection is the major factor responsible for the immunosuppression.

Table 2 Delayed Hypersensitivity Skin Reactions to 3 Antigens in Patients and Controls

	Number of positive reactions per subject			
	0	*1*	*2*	*3*
Patients	7	4	0	0
Controls	0	4	6	1

Chyluria is usually caused by an obstruction to the drainage of lymph into the thoracic duct, resulting in dilatation and rupture of abdominal lymphatics into the urinary tract with retrograde lymph flow (Karanjavala, 1970). Chyle is thus lost from the body and functionally a situation similar to surgical fistulous thoracic duct drainage results. Thoracic duct drainage, sometimes used for immunosuppression in man, results in lymphocytopenia and hypogammaglobulinaemia, since lymphocytes (predominantly T cells) and immunoglobulins are lost from the body (Graber *et al.*, 1969; Machleder and Paulus, 1978; Kaplan, 1979).

Chyluria is functionally also similar to intestinal lymphangiectasia, another condition produced by obstruction to abdominal lymphatics and with retrograde lymph flow and escape of chyle from a mucosal surface. Patients with intestinal lymphangiectasia also have a decrease in circulating T lymphocytes, depressed cell-mediated immunity and hypogammaglobulinaemia (Weiden *et al.*, 1972; Tift and Lloyd, 1975; Vardy *et al.*, 1975; Herzog *et al.*, 1976).

Abdominal lymphatics drain an area rich in IgA producing cells and thoracic duct lymph has IgA concentrations one-third to one-half of that present in serum, while IgG levels are only one-tenth of serum values (Graber *et al.*, 1969). Patients undergoing long-term thoracic duct drainage have a greater reduction of IgA than IgG levels (Machleder and Paulus, 1978). A generalised reduction in serum immunoglobulins was not present in the patients in this study but serum IgA levels were low.

The similarity to conditions mentioned above suggests that the suppression of delayed hypersensitivity in chyluria is due to T cell deficiency, resulting from lymphocyturia. However, a residual effect of past filarial infection cannot be completely excluded as a minor factor contributing to the immunosuppression in these patients. In this context it would be interesting to know the immune status in cases of non-filarial chyluria. The rarity of this condition and the difficulty in proving that chyluria, in a patient from an area endemic for filariasis, is of non-filarial origin prevented us from studying this condition.

The absence of increased susceptibility to infection in patients with chyluria is similar to that observed in intestinal lymphangiectasia (Tift and Lloyd, 1975) and sufficient residual immune function to cope with infection is apparently present. T cell deficiency in experimental animals causes an increased susceptibility to glomerulonephritis (Hoffsten *et al.*, 1977) and membranous glomerulonephritis has been reported in a patient with intestinal lymphangiectasia (McDonagh *et al.*, 1965). While none of the patients in this study had evidence of glomerulonephritis, glomerular lesions have been reported in some patients with chyluria (Date *et al.*, 1979).

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Case Reports

Conservative Management of Renal Adenoma *v.* Adenocarcinoma

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The incidental finding of an asymptomatic, small renal neoplasm presents a problem in both diagnosis and management. Although nephrectomy is usually carried out, a more conservative approach may be warranted in selected patients.

Case Report

A 55-year-old diabetic female presented with hypertension. An excretion urogram revealed a right renal mass indicated as solid by grey-scale ultrasound. A renal arteriogram demonstrated a well demarcated 2 cm vascular cortical neoplasm (Fig.) suggesting a diagnosis of renal adenoma. The left kidney was normal. At operation a solitary renal mass was found and removed by wedge resection which included a 2 cm margin of normal parenchyma. Pathological investigation revealed a yellow-brown circumscribed renal carcinoma.

A renal arteriogram 2 years after operation revealed no recurrent tumour and the patient remains well after 3 years.

Comment

Renal tumours measuring less than 3 cm have less potential for spread (Bell, 1938). However, no pathological, histochemical, immunological or ultrastructural features reliably distinguish renal adenocarcinoma from adenoma (Bennington and Beckwith, 1975). Incidental renal adenomas are more common than carcinomas at autopsy and occur most frequently after 40 years of age. Increased longevity and improved diagnostic methods, such as computerised tomography, will improve the detection rate of asymptomatic lesions. The benign or malignant nature of such tumours is of obvious practical concern.

Surgery is the treatment of choice, although the extent required is not known. Small (2 cm or less), localised and readily accessible solid renal neoplasms are unlikely to recur locally or metastasise if completely removed. Conservative excision therefore appears indicated in selected patients.

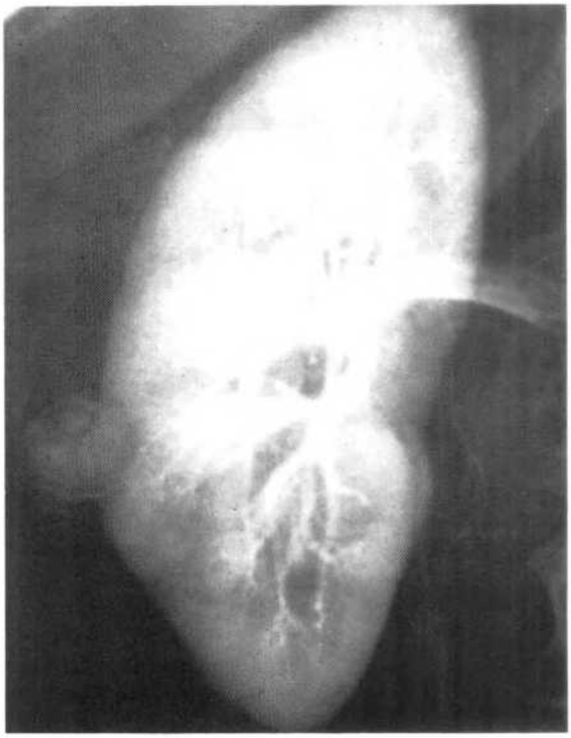

Fig. Arterial phase of a selective right renal arteriogram showing a round vascular cortical neoplasm measuring 2 cm.

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Solitary Vaginal Metastasis from Renal Carcinoma (Concurrent with Endometrial Carcinoma)

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This case had 2 unusual aspects: (1) the renal carcinoma presented with bleeding from a vaginal metastasis, and (2) an endometrial carcinoma was found concurrently.

Case Report

A 47-year-old woman was admitted with vaginal bleeding of 2 weeks' duration. Previously her periods had been regular, with normal flow, and she had had no hormonal treatment. The only relevant past medical history was hypertension of 3 years' duration which was treated by methyldopa.

On vaginal examination a friable haemorrhagic bulge, 3 cm in diameter, was noted on the distal right lateral wall of the vagina. The uterus was slightly enlarged and the adnexae appeared normal. Excision of the vaginal lesion and uterine curettage were performed. Histology of the vaginal lesion showed a poorly differentiated renal carcinoma with areas of clear cell appearance (Fig.). The endometrium showed adenomatous cystic hyperplasia with epithelial atypia consistent with carcinoma *in situ*. Intravenous urography showed displacement of the upper calices of the right kidney by a round mass. Chest X-ray, liver scan and bone survey were negative. Liver function tests were normal. Urine: microscopic haematuria; ESR: 47 mm at first hour. Right nephrectomy was carried out with the lesion occupying the upper pole of the kidney. Microscopically the tumour was a renal clear cell carcinoma with penetration of the capsule and the wall of the renal vein.

Medroxyprogesterone, then CCNU and testosterone were given after the operation but the patient developed liver metastases and died 6 months later. There was no post mortem examination.

Comment

The incidence of apparently solitary metastasis from renal carcinoma is uncommon, being 1 to 3%. Vaginal metastasis is rare: 50 previous cases have been reported in the literature (Nocks and Newman, 1970; Tolia and Whitmore, 1975). The similarity between the renal clear cell appearance and the primary mesonephric adenocarcinoma of the vagina may present some difficulties in the histological diagnosis of metastatic renal carcinoma to the vagina. In such a case, urological investigations must be carried out.

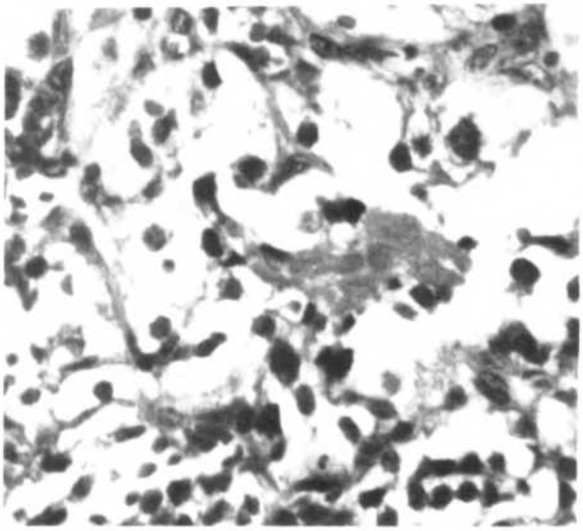

Fig. H and E (× 400).

The association between renal carcinoma and adenocarcinoma of the uterus is of special interest since it raises the possibility of a common hormonal aetiology (? oestrogen excess). This may be reinforced by experimental studies and the use of progesterone in the treatment of metastatic carcinoma of the kidney and the endometrium (Bloom, 1972).

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Metastases to the Penis from Carcinoma of the Prostate

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Case Report

A 78-year-old circumcised man presented with severe pains in the pelvic region and urinary retention. Oestrogen treatment had begun 2 years earlier for a histologically confirmed carcinoma of prostate (Fig. 1). On admission the entire penis was infiltrated by a soft tumour mass causing a priapism-like appearance. Rectal examination revealed an enlarged and hard prostate. Radiological examination showed metastases in the pelvic and lumbar vertebrae. In spite of the clinical findings the serum acid and alkaline phosphates were normal. A biopsy of the penile tumour and bilateral orchiectomy were performed. Histological examination of the penile biopsy showed metastases of a well differentiated carcinoma (Fig. 2). Radiotherapy and 5-fluorouracil treatment were started but there was no improvement and the patient died 4 months later.

Comment

Metastases to the penis from carcinoma of the prostate are rare (Abeshouse and Abeshouse, 1961; Wolf and Madsen, 1968). A patient with penile metastases has a very poor prognosis and the results with current forms of treatment are discouraging.

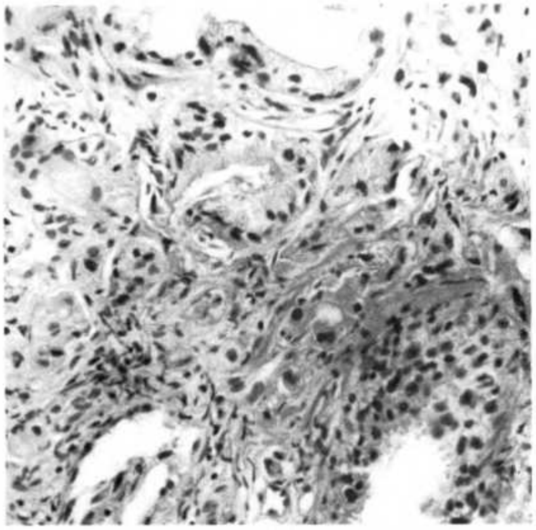

Fig. 1 Carcinoma of the prostate (H and E × 200).

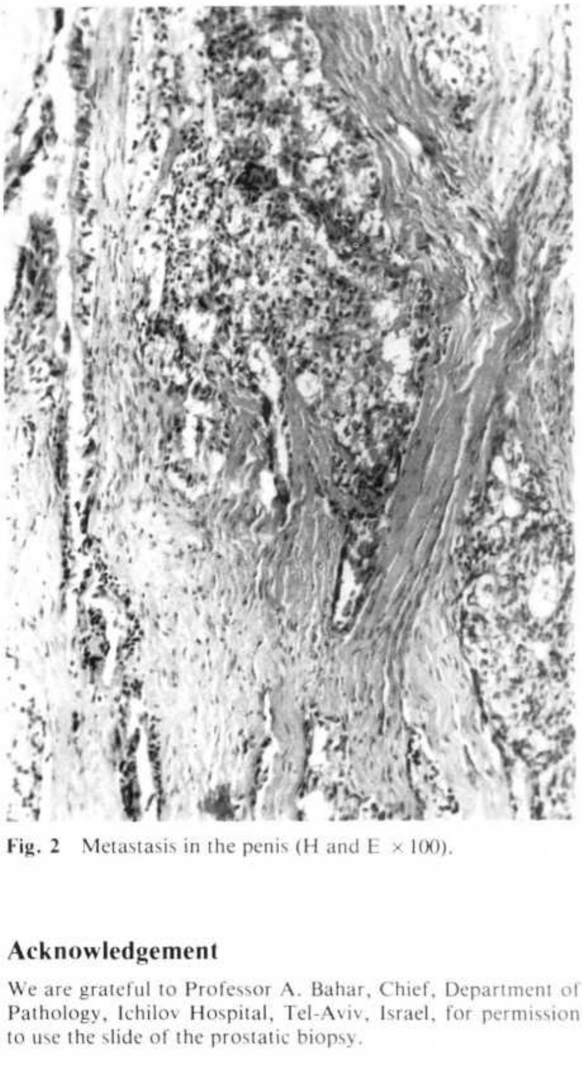

Fig. 2 Metastasis in the penis (H and E × 100).

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Priapism of the Clitoris

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Priapism in men has been described by many authors (Smith and Bonacarti, 1964; Grace and Winter, 1968) in relation to sexual over-indulgence, sickle cell anaemia, leukaemia, neoplasms, diseases of the central nervous system, schizophrenia, tumours of the kidney, bladder or urethra, and endoscopic procedures in the posterior urethra.

This report concerns a case of priapism of the clitoris and is the first to be described in the English literature. The cause was retrograde neoplastic embolisation of the corpora cavernosa of the clitoris by cervical carcinoma (clinical stage 4) through the internal pudendal veins.

Case Report

M.O.F., a 49-year-old female, had profuse vaginal bleeding with loss of weight and weakness in May 1976. She attended hospital in January 1977, when a diagnosis of stage 3 cervical carcinoma was made. She was referred to the Urology Department for routine cystoscopy and we found signs of bladder invasion; the tumour was therefore reclassified as stage 4. The intravenous urogram showed non-function of the right kidney. X-ray of the chest was normal.

Cobalt teletherapy was started and one week later she complained of pain in the genital area. We found the clitoris indurated and enlarged to 9 cm (Fig.). We diagnosed priapism and to relieve her pain the clitoris was removed under epidural anaesthesia.

The histopathology report described thrombosis of the corpora cavernosa with metastatic anaplastic carcinoma.

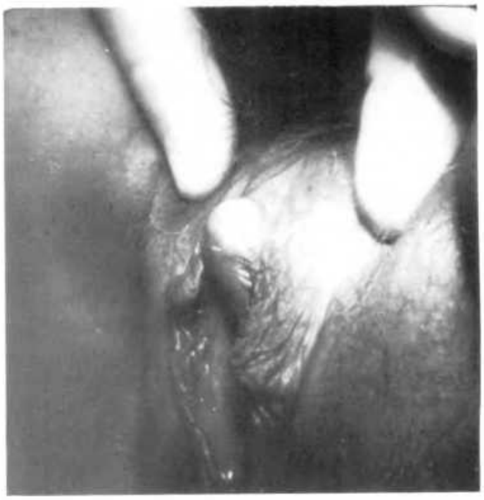

Fig.

The patient received 6000 rads of Co^{60} teletherapy but her neoplastic disease progressed and she died 15 months later.

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Urinary Retention Secondary to Simple Ureterocele in an Adult

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Most simple ureteroceles in adults are incidental findings discovered on urography. We have recently seen an adult male with marked voiding dysfunction which proved to be due to a redundant simple ureterocele.

Case Report

A 32-year-old man sought attention because of a markedly weakened urinary stream. This symptom was of abrupt onset and was associated with severe hesitancy, intermittency, and straining to void, which produced only a few drops of grossly bloody urine. Intravenous urography (Fig.) demonstrated the typical intravesical filling defect associated with a simple ureterocele, along with mild, distal ipsilateral ureterectasis. No calculus was present within the ureterocele. Cystourethroscopy revealed that the ureterocele involved the entire right hemitrigone; the bladder neck and prostate were non-obstructive and it was thought that the voiding symptoms were due to prolapse of the large ureterocele into the vesical neck. Excision and ureteric reimplantation were performed without difficulty, following which the patient resumed normal voiding.

Comment

Symptomatic ureteroceles in adults are uncommon; when difficulty does occur, flank pain is the usual complaint (Madsen *et al.*, 1975). Prolapse of the ureterocele into the proximal urethra has been demonstrated radiographically in 2 previous instances (Poznancki *et al.*, 1968; Parsons and Malpass, 1973) and is assumed to be the cause of the voiding dysfunction in our patient. Treatment of the symptomatic adult ureterocele remains controversial. To avoid the potential complication of reflux, which is frequently associated with simple incision of ureteroceles, excision combined with reimplantation has been advocated (Hutch and Chisholm, 1966). This latter approach was adopted in our patient with a satisfactory result.

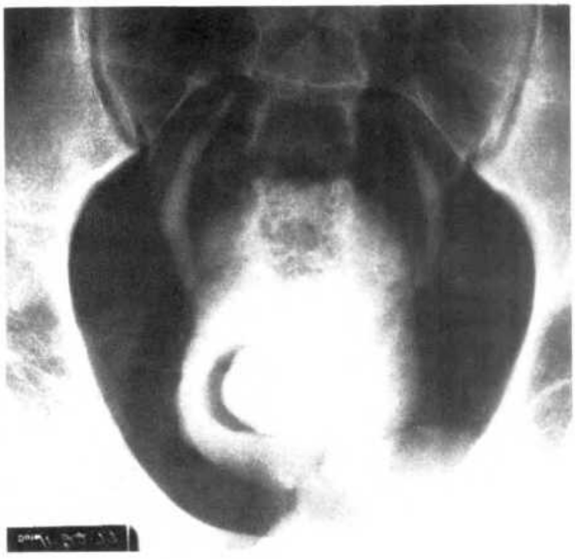

Fig.

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Points of Technique

A Simple Technique for Handling the Kidney Graft during Transplantation

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Handling the kidney graft during the vascular anatomoses may be troublesome, especially in adipose patients and if the vessels of the transplant are short. To avoid a secondary period of warm ischaemia, the kidney should be cooled, which may be difficult under similar conditions.

During the last 6 years I have used a simple tool to handle the kidney transplant during operation. The kidney is placed in a 12 cm broad and about 20 cm long plastic bag (used for sterilising the suction tubing and nozzle), made of rather tough polyethylene. A 3 cm hole is cut in the bottom of the bag and the artery and the vein pulled out through the hole (Fig.). In this way the vessel anastomoses can be made keeping the ureter and the hilar tissues out of the way. The kidney is fixed by the bag, it can easily be moved in all directions, and exactly enough traction is applied to the vessels without disturbing retractors or assistants' hands. The kidney is kept safely cool by sterile ice placed in a towel above and partly around the kidney. The vessel anastomoses can be carried out without any necessity to hurry. When the vessel anastomoses are completed, the plastic bag is cut open and removed. The plastic bag can also be used when the renal vessels have to be repaired or multiple arteries or veins united prior to implantation of the graft.

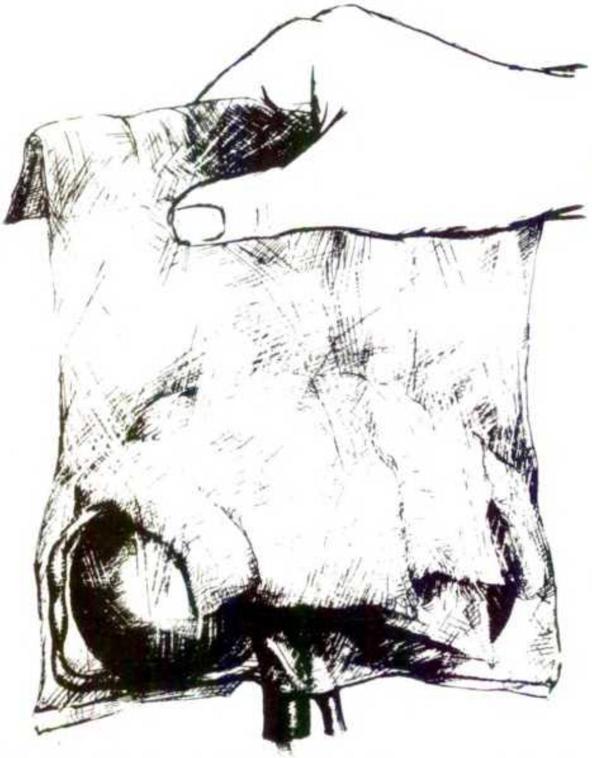

Fig. The kidney graft is placed in a plastic bag and the vessels protrude through a hole cut in the bottom of the bag.

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Author's Follow-up

Ultrasound in Renal Disease. A Review after 6 Years

K. J. W TAYLOR, *Department of Diagnostic Radiology, Yale-New Haven Hospital, New Haven, Connecticut 06504, USA*

Since our original study (Taylor and Kraus, 1975) there have been dramatic improvements in the ultrasonic demonstration of both the anatomy and the pathology of the kidney. The renal pyramids, cortex, arcuate and main renal vessels are routinely imaged. In demonstration of renal pathology, ultrasound scanning is frequently complementary to the functional changes seen by urography or scintigraphy. The most frequent indication for ultrasound scanning is acute renal failure, when ultrasound is highly reliable in demonstrating or excluding the presence of obstructive uropathy. In the presence of a non-visualised kidney on urography, ultrasound demonstrates the anatomy of the kidney or its replacement by cysts, tumours or a hydronephrotic sac. When a mass is shown on urography, ultrasound indicates whether this is solid or cystic and permits accurate localisation of the lesion for aspiration or biopsy procedures. In patients with polycystic disease, one can document not only the cysts in the kidney but also their concomitant occurrence in the liver, spleen or pancreas. In a continuing study of families with polycystic disease, we have shown that ultrasound is more sensitive than urography for detecting the smallest cyst at the earliest signs of the disease in infants and children.

The advent of real-time ultrasound equipment has greatly facilitated examination of the kidneys in restless children and has provided a means for obtaining automatic, high-resolution scans by the less experienced operator. Much of this real-time equipment is portable and is well suited to the diagnosis of neonates in incubators or anuric patients in intensive care.

Pre-natal and non-invasive post-natal diagnosis of renal anomalies is now common. Obstructive uropathy secondary to posterior urethral valves can now be diagnosed pre-natally and treated. Abdominal masses in the neonate can also be rapidly characterised by portable ultrasonography.

In the severely injured patient, ultrasound provides a means for rapidly scanning the entire abdomen and pelvis which is rivalled only by computerised tomography, the latter being much less universally available. Much of the potential of ultrasound examination in trauma has yet to be realised, but since it displays the anatomy of the kidney, ultrasound can be valuable in assessing the extent of trauma to that organ.

Inflammatory masses of the kidney can be imaged, including renal carbuncles and perirenal abscesses. Those that require drainage can be so drained under ultrasound guidance. Ultrasound imaging is useful in the management of the transplanted kidney, in order to detect the changes of rejection, obstruction or the presence of surrounding fluid collections such as lymphocele, urinoma or abscess.

The last 6 years have witnessed a dramatic increase in the use of ultrasound imaging of the kidney. As the modality gains more acceptance by radiologists and surgeons, further utilisation can confidently be expected.

Reference

Taylor, K. J. W. and Kraus, V. (1975). Grey-scale ultrasound imaging: assessment of acute hydronephrosis *British Journal of Urology*, **47**, 593-597.

British Journal of Urology (1981), **53**, 394
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Notices

Institute of Urology (University of London) in association with St Peter's Hospitals

Ten Week Course on The Scientific Basis of Urological Practice

25 January to 2 April 1982

A full-time non-residential course covering all aspects of urological practice undertaken at the Institute and its associated St Peter's Hospitals.

There will be discussions of the techniques used and the research being undertaken. Operations will be demonstrated by means of closed circuit TV.

The course is designed for specialists in the field and those undergoing training in urology. It has been approved under the Advanced Postgraduate Training Scheme.

Closing date for applications: 1 December 1981.

Fee: EEC and UK based applicants £600.
Applicants from all other countries £1200.

For further details and application form contact The Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01-836 5361.

South African Urological Congress

Sun City. Bophuthatswana, South Africa. 21-26 March 1982.

Further particulars from: Dr P. J. Reyneke, P.O. Box 44004, Linden, 2104, Republic of South Africa.

Second Congress of the International Society of Urologic Endoscopy

Bristol. 8-11 September 1981

Further particulars from: Conference Services Limited, 3 Bute Street, London SW7 3EY. Tel. 01-584 4226.

Eighth Course of Urology for Postgraduates

Madrid, Spain. 2-6 November 1981

Main topic: Reconstructive Surgery of the Genitourinary System.

Further particulars from: Secretary, Service of Urology, C. S. La Paz, Paseo de la Castellana 261, Madrid 34, Spain.

Book Received

Transurethral Surgery. Edited by L. F. Greene and J. W. Segura. Pp. xv+400. Philadelphia: W. B. Saunders. 1979. Price £25.25.

Book Reviews

Recent Advances in Sexually Transmitted Diseases. Edited by J. R. W. Harris. Second edition. Pp. xii+281. Edinburgh: Churchill Livingstone. 1981. Price £18.00.

This book comprises 22 review articles, written by an international group of authors, covering topics of current importance. The importance of chlamydial, mycoplasmal and *Candida* infections as aetiological agents in prostatitis, epididymitis and the urethral or frequency/dysuria syndrome may make the chapters on these topics of special interest to the urologist, but the book is really intended for the specialist in genitourinary medicine.

Clinical Practice in Sexually Transmissible Diseases. D. H. H. Robertson, A. McMillan and H. Young. Pp. x+458. Tunbridge Wells: Pitman Medical. 1980. Price £27.00.

The authors state that this book is written primarily for those actively engaged in the clinical practice of venereology but it is intended also to be a reference book for others who practise, to some extent anyway, sexual and reproductive medicine, especially in adolescents and young adults.

The authors have considered not only the clinical and microbiological aspects of the subject but also the psychological aspects inseparable from all physical sexual problems, and stress the need for the concern and compassion essential for the management of patients with venereal disease.

Atlas of Renal Pathology. (Current Histopathology Series: Volume 2). R. A. Risdon and D. R. Turner. Pp. 90. Lancaster: MTP Press. 1981. Price £17.50.

This attractive book of large format and less than 100 pages is one of a new series of atlases on systemic pathology under the general editorship of Professor Gresham. The aim of the authors is to provide a simple, straightforward guide for general pathologists who do not have a specialised knowledge of the subject, and for pathologists in training. Tumours of the kidney have been omitted on the grounds, presumably, that there already exist excellent atlases of tumour pathology.

The illustrations in this atlas are on the whole of high quality: most of them are colour photomicrographs. The colour rendering is somewhat variable and some of the electron-micrographs are of rather poor quality and are uninformative. It is doubtful if the novice would make very much of them. There is a fairly comprehensive coverage of pathological processes and Drs Risdon and Turner provide a succinct and informative text with well chosen references to key papers, which adds considerably to the book's value as an atlas.

There is no doubt that the authors have produced a book which will be useful to the busy general pathologist and trainee. Physicians and surgeons with an interest in renal pathology might also study this book with pleasure and profit.

Current Diagnostic Pediatrics. Diagnostic Imaging of the Kidney and Urinary Tract in Children. Edited by A. R. Chrispin, I. Gordon, C. Hall and C. Metreweli. Pp. xviii + 206. Berlin, Heidelberg, New York: Springer-Verlag. 1980 Price DM 118.00: US $69.70.

This book is probably unique in its brief and certainly novel in its philosophy. The authors, all of whom work in one renowned paediatric centre and each of whom has his or her own particular imaging interest, must be congratulated on having combined to present a concise, well balanced but determined approach to this subject.

Conventional radiology and the newer imaging modalities, isotopes, ultrasound and CT, are placed very firmly in a clinical context which is vital to their best use. Diagnosis of urinary tract pathology in the child is an area where newer imaging techniques have changed traditional practice. One is always acutely aware of the necessity to reduce radiation to a minimum in children and now we are presented with 2 new complementary techniques which fulfil this criterion and offer not only ideal imaging of renal morphology which is independent of function (ultrasound) but also a very sophisticated assessment of that function (isotopes). The place of CT scanning is not yet fully evaluated, but a small but significant role will undoubtedly emerge.

Every page is filled with important diagnostic information together with much background medicine, pathology and embryology. The text has been carefully honed and is complemented by numerous useful images and figures. A great deal of paediatric experience is encompassed in these relatively few pages.

This book is essential reading for any urologist working with children who, at least in current diagnostic imaging terms, are most certainly not just small adults.

Nephrolithiasis. (Contemporary Issues in Nephrology, Volume 5). Edited by F. L. Coe, B. M. Brenner and J. H. Stein. Pp. 275. Edinburgh: Churchill Livingstone. 1980. Price £19.00.

This book contains contributions by 16 distinguished American physicians. Written with great clarity, all of the chapters except for the one on crystal epistaxis have a practical orientation. The medical aspects of stone disease are comprehensively covered in a text commendably up-to-date in a changing field.

Individual metabolic abnormalities are dealt with, together with their treatments, and a wealth of literature is quoted in relation to each. The format does not allow a general critique of therapeutic trials and some discussion of the difficulty in avoiding unsought patient selection and establishing true control populations would have been welcome.

The surgery of stone receives little space, but any urologist undertaking metabolic survey and medical treatment of stone patients will find benefit in this well laid out and highly readable text.

Urazy Moczowodow (Ureteric Injuries). Stefan Wesolowski. Pp. 352 + 217 illustrations. Warszawa: Panstwowy Zaklad Wydawnictw Lekarskich.

This monograph by the most renowned Polish urologist, who incidentally is an honorary member of BAUS, is in Polish. There are only 1½ pages in English (the summary at the end) and it is therefore not likely to be seen by more than a few readers of this Journal. However, it is such a beautifully produced book, with excellent illustrations and X-rays, that its publication must be recorded as an outstanding record of personal experience in the treatment of ureteric injuries

The English summary states that the cases consist of 171 patients with 205 ureteric injuries, 34 being bilateral cases. There is a very brief summary of the cause and treatment of each case in Latin before the more detailed description in Polish. The combination of the Latin summaries and the illustrations is remarkably successful in transmitting the essential features of the cases.

The cases are grouped according to the speciality involved in the causation of the injuries—urology, gynaecology, obstetrics, radiotherapy, general surgery, and then finally injuries caused by external trauma. The final chapter is devoted to the detailed operative treatment of the injuries. At the end of each chapter there is an extensive list of references in their original languages.

This book is worth just seeing as an obviously outstanding monograph by a world figure in urology.

IMPORTANT ANNOUNCEMENT

During April Calcisorb from Riker Laboratories will replace Whatman Sodium Cellulose Phosphate which is being discontinued. This is a product name and packaging change only. Formulation and dosage will remain the same.

CALCISORB
sodium cellulose phosphate

For the treatment of idiopathic hypercalciuria associated with recurrent formation of renal calculi.

Prescribing information. Composition: Each 5g sachet contains 4.7g sodium cellulose phosphate. **Indications:** Calcisorb is used to diminish calcium absorption from the diet: 1) in the treatment of hypercalciuria and recurrent formation of renal stones 2) in osteopetrosis 3) as a basis of a test for calcium absorption. Other possible uses are: 1) treatment of idiopathic hypercalcaemia of infancy 2) treatment of hypercalcaemic sarcoidosis 3) treatment of vitamin D intoxication. **Dosage and administration:** Adults: 15g daily, divided as three 5g doses with meals. Children: 10g daily, divided as three doses with meals. The required dose should be dispersed in water and taken orally. Alternatively the powder may be sprinkled onto food. **Side-effects:** Side-effects are rare. Isolated cases of diarrhoea have been reported. One patient with mild renal disease, developed a moderate magnesium deficiency. This was readily corrected by halving the dose. **Caution:** No signs of calcium deficiency have been reported during the continuous use of cellulose phosphate for up to 11 years. This theoretical hazard is particularly relevant to pregnancy, but in view of the absence of data on the effect of cellulose phosphate on calcium levels in pregnant women it is recommended that treatment is discontinued during pregnancy and lactation. Likewise growing children should be prescribed Calcisorb only at the discretion of a senior physician and under his direct supervision. **Contra-indications:** Renal failure. Congestive heart failure and other conditions in which a low sodium intake is essential. **Further Information:** Calcisorb should be used in conjunction with a low calcium diet in which dairy products in particular are severely restricted. **Basic NHS price:** Packs of 100 x 5g sachets: £17.35. **Product licence number:** 68/5900. *Calcisorb, Riker, 3M* trade marks. Further information is available on request. Whatman is a trademark of Whatman Ltd.

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TECHNICAL DATA

STERILISED ABSORBABLE SYNTHETIC SUTURE COATED POLYGLACTIN 910 VICRYL*

Presentation The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form.

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption.

Action Two important characteristics describe the in vivo behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained.

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated.

Dosage and Administration
By implantation.

Contraindications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of VICRYL (Polyglactin 910) and Coated VICRYL Sutures in neural tissue and in cardio-vascular tissue have not been established.

Pharmaceutical Precautions
Do not re-sterilise.

Legal Category P Pharmacy medicine sold to surgeons and hospitals through surgical dealers.

Package Quantities Various lengths of material packaged in sealed aluminium foil sachets. This primary pack is contained in a peel-apart secondary pack. The unit of sales is 12 packs contained in a film wrapped drawer style carton.

Adverse Reactions No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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The British Journal of Urology welcomes original contributions on urological subjects from all parts of the world. Papers are accepted for consideration on the understanding that their contents have not been published in whole or in part elsewhere, that they are subject to editorial revision, and that the Editor is responsible for the order of publication. Papers on nephrology, of interest to the urological surgeon, are welcome. When relevant, authors must include a statement on the ethical aspects of their research.

Manuscripts. Papers should be submitted in Journal style. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. **Two copies of the manuscript and illustrations should be submitted** and the author should retain a copy for reference. **All authors must give signed consent to publication.**

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

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Abrams, P. H., Roylance, J. and Feneley, R. C. C. (1976). Excretion urography in the investigation of prostatism. *British Journal of Urology*, **48**, 681-684.

References to books should be set out as in the following example:

Britton, K. E. (1979). Radionuclides in the investigation of renal disease. In *Renal Disease*, ed. Black, D. and Jones, N. F. Fourth edition. Chapter 10, pp. 270-304. Oxford: Blackwell.

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Abbreviations and units. All measurements should be expressed in S.I. units except blood pressure which will continue to be expressed in mmHg. For more detailed recommendations authors may consult the Royal Society of Medicine publication entitled *Units, Symbols and Abbreviations: A guide for Biological and Medical Editors and Authors.*

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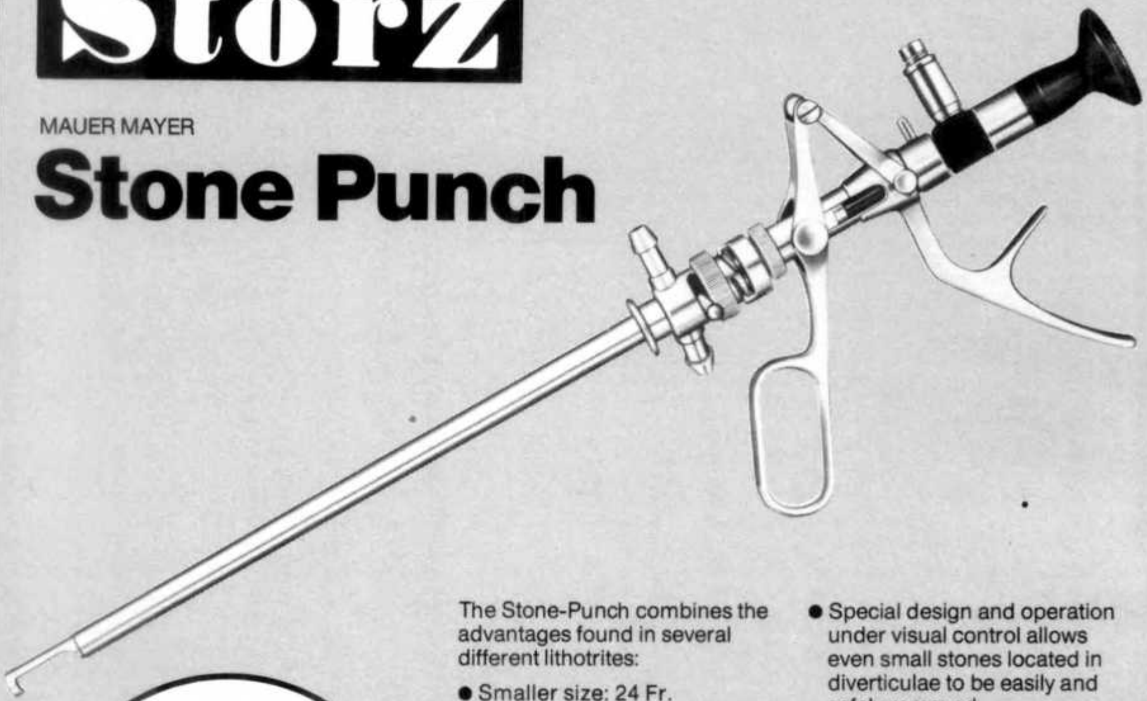

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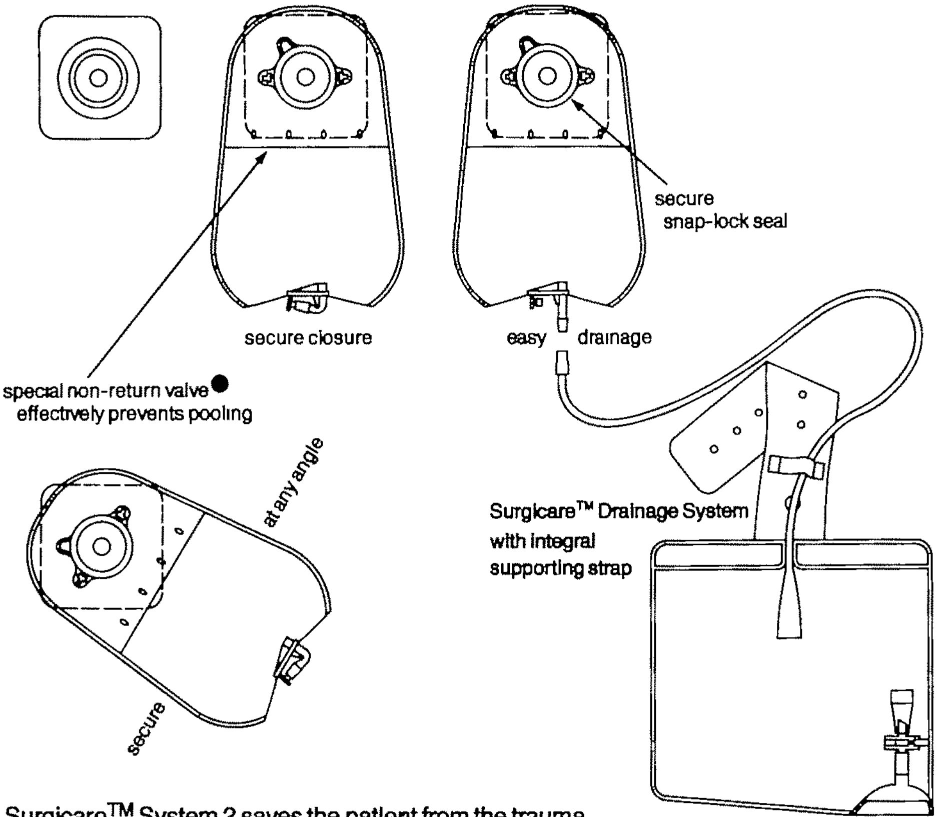

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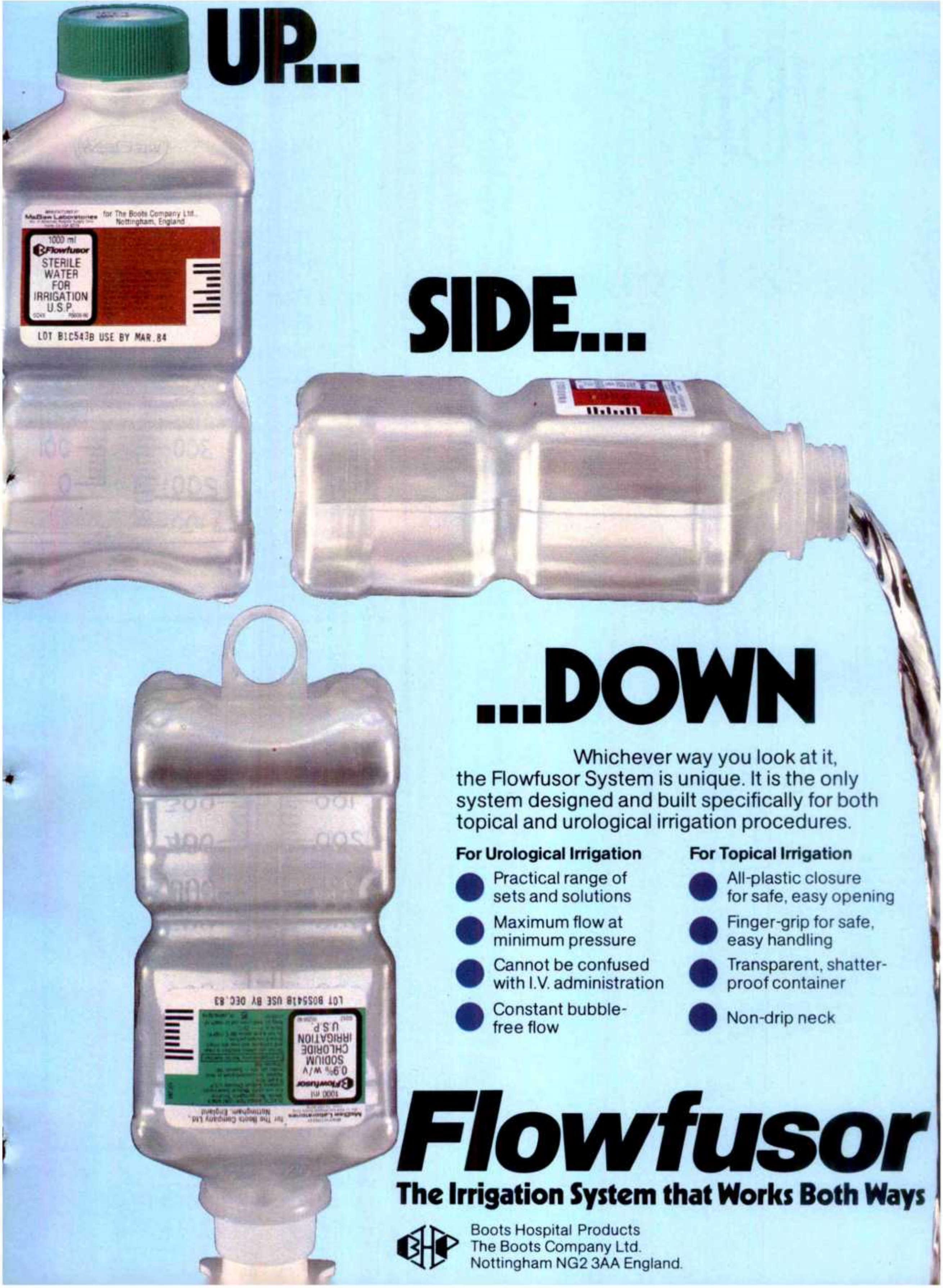
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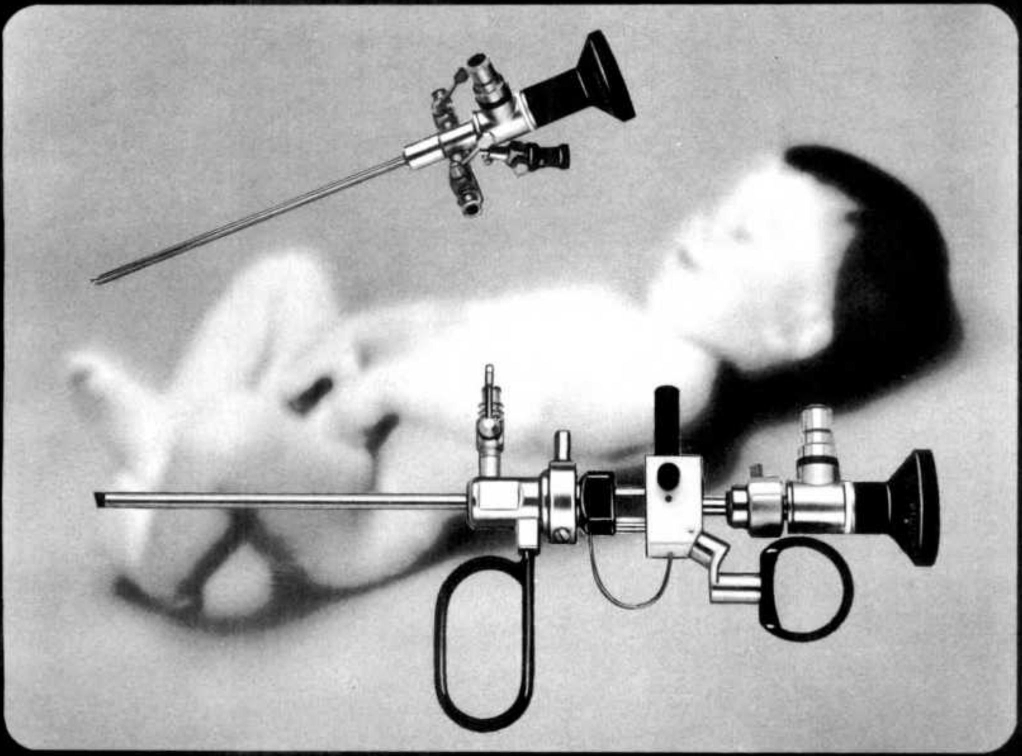

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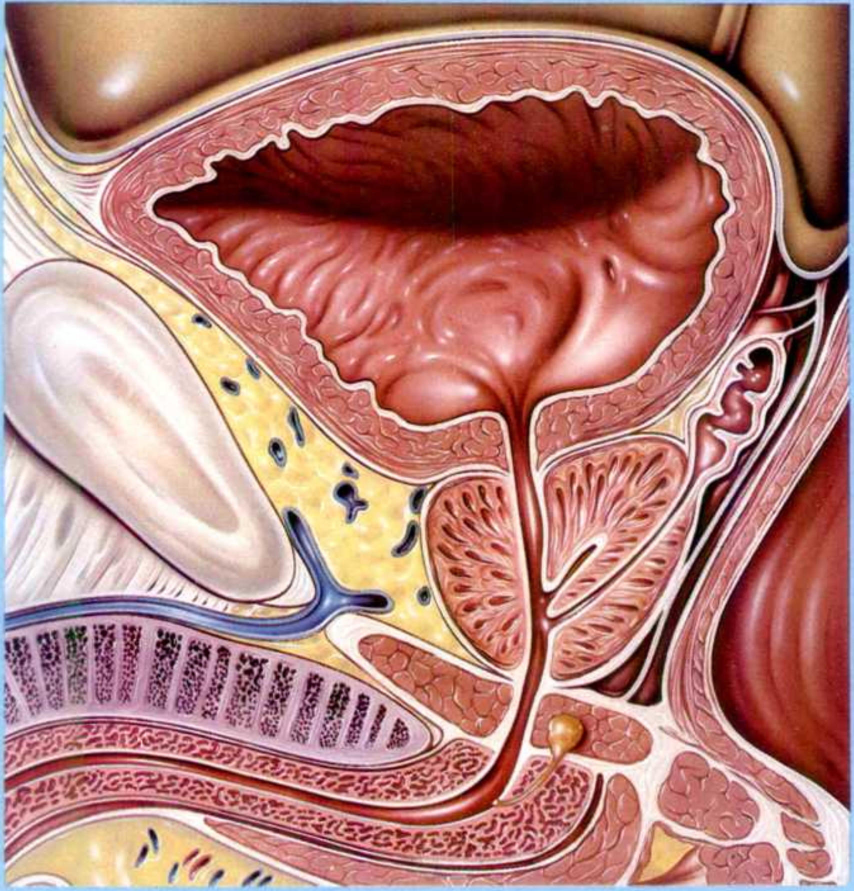

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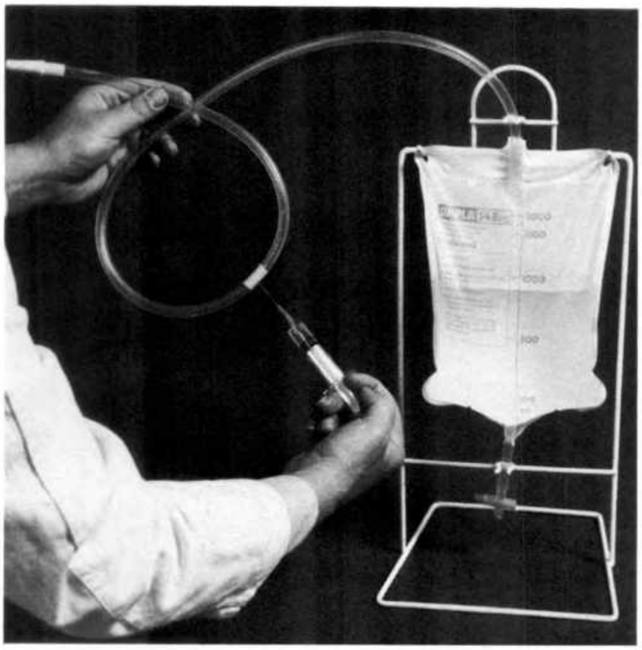

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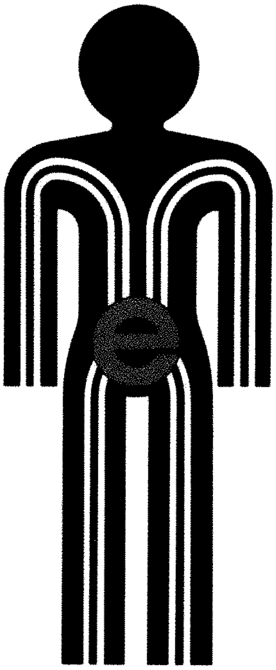

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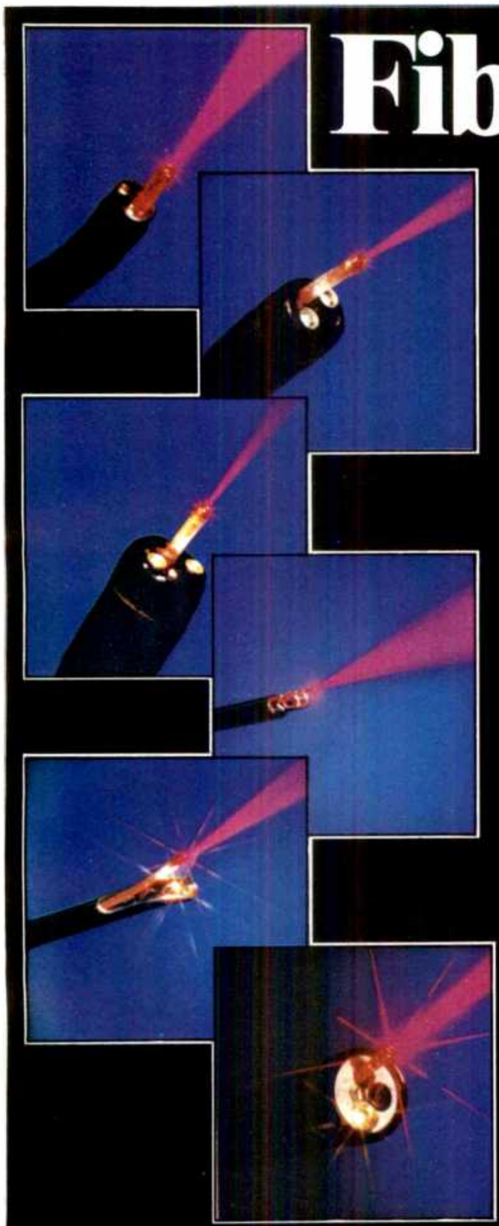

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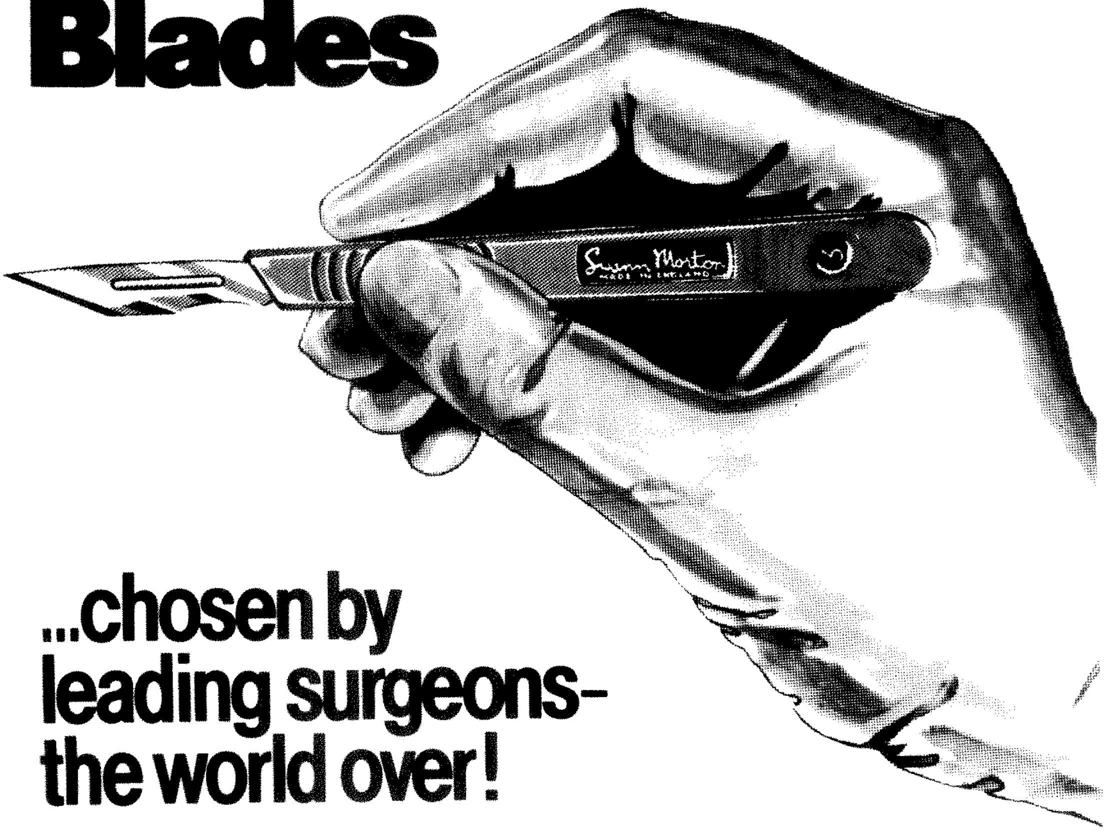

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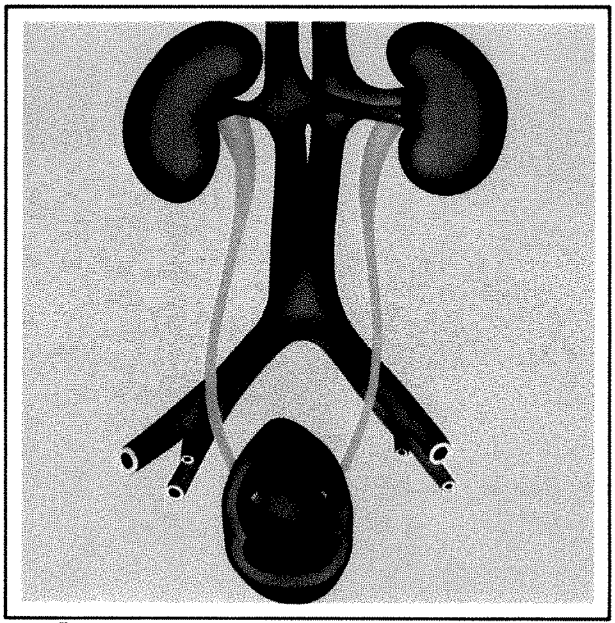

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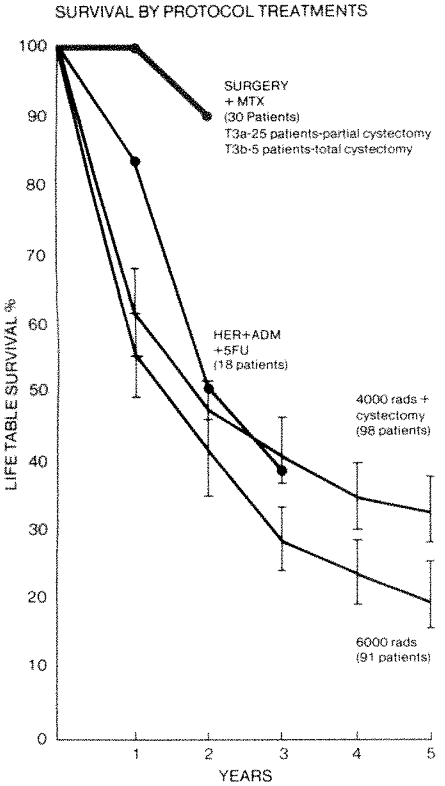

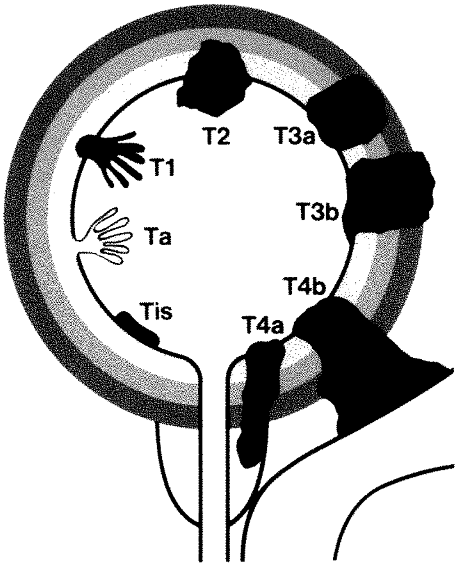

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1. Smith PH. Paper read at *International Symposium on Methotrexate*, London 1979. *Cancer Treatment Reports*. In Press.
2. Socquet Y. *Ibid.*
3. Calvert AH and Turnbull CP. *Cancer Treatment Reports*. In Press.

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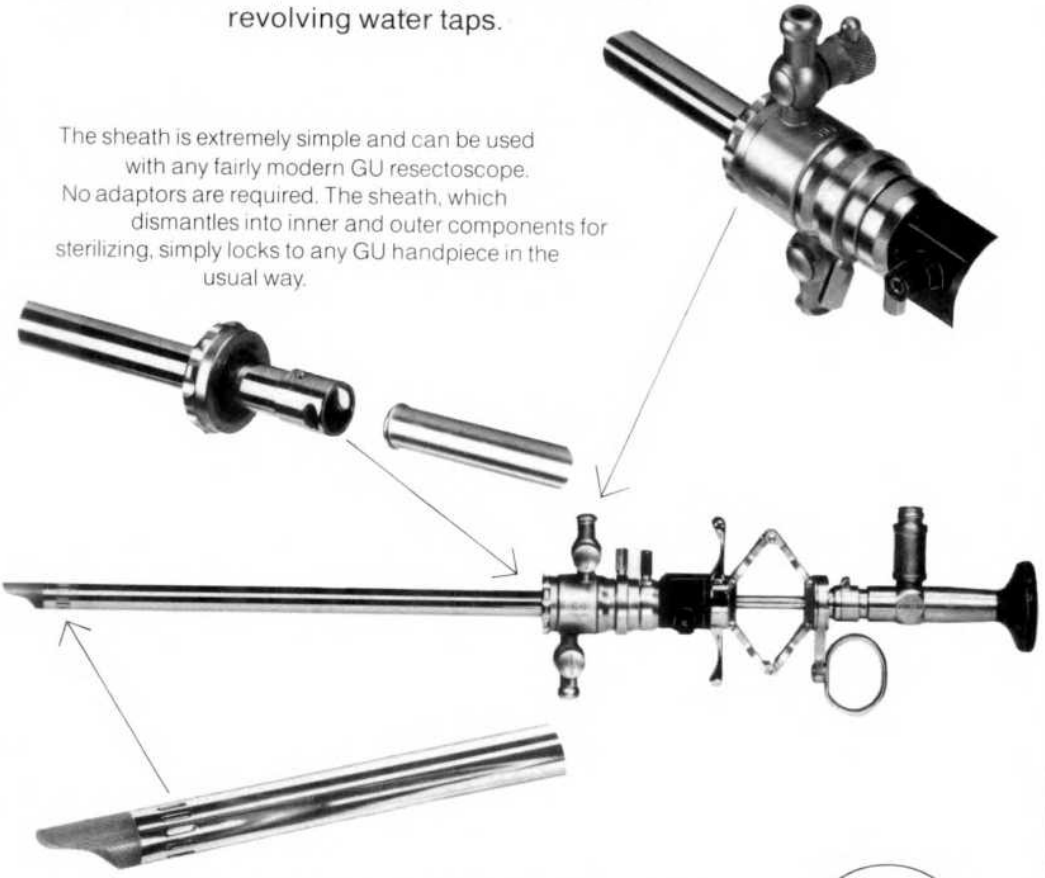

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The Urological Complications of 1000 Renal Transplants

A. R. MUNDY, M. L. PODESTA, M. BEWICK, C. J. RUDGE, F. G. ELLIS

and the Physicians and Surgeons of the Renal Units of the S.E. and S.W. Thames Regions *

Summary—Two hundred and one urological complications have been diagnosed and treated in 123 transplant recipients in a series of 1000 consecutive renal transplant operations (overall incidence 12.5%). Obstructive uropathies and urinary fistulae accounted for 95% of these complications and all of the mortality (22%). Details of management and patient and graft survival are given. A relationship between mortality from a urological complication and steroid dosage was found. A 30% incidence of recurrent or secondary urological complications was also noted with correspondingly worsened prognosis. Early diagnosis followed by early aggressive surgical treatment is advocated.

The urological complications of renal transplantation are important for 3 reasons. Firstly, there are the general urological implications of a compromised solitary kidney. Secondly, they must be distinguished from graft rejection as a cause of declining renal function. Thirdly, they are potentially very serious since the patients are receiving immunosuppressive therapy with consequent poor healing and predisposition to local and systemic infection. This report concerns the urological complications seen in 1000 consecutive renal transplants performed between May 1967 and December 1979.

Patients and Methods

One thousand renal transplants were performed on 826 patients with a mean age of 39.5 years (range 4-71) and a male to female ratio of 2:1. Eight hundred and twenty kidneys came from cadavers and 180 from living related donors. There were 826 first transplants, 158 second transplants, 14 third transplants and 2 fourth transplants. Eight per cent of the recipients were children. The recipient pool included 54 patients with diabetes mellitus and 50 patients who were Australia Antigen positive. Two hundred and thirty-two of the recipients had been regarded as unsuitable for renal transplantation at other transplant centres. All patients received azathioprine and prednisolone starting at the time of operation and, in addition, antilymphocyte globulin was used in some patients. For purposes of analysis patients were classified as having had "high-dose" or "low-dose" steroid regimes according to whether they received more or less than 0.3 mg prednisolone/kg body weight/day or its equivalent for other steroids at maximal routine dosage. By this criterion 713 recipients received "high-dose" regimes and 287 recipients received "low-dose" regimes.

Primary ureteroneocystostomy was performed in 994 cases. The nipple technique of Paquin (1959) was used in 196 of the earlier transplants. More recently the preferred method (772 cases) has been the tunnel technique of Politano and Leadbetter (1958). The extravesical technique of Woodruff *et al.* (1969) was used in 26 cases. The transplant ureter did not extend below the lower pole of the kidney on 6 occasions and ureteroneocystostomy was not possible even with a Boari flap; 4 of these had a primary ureteroureterostomy and in 2 cases a pyeloureterostomy was performed, with splinting of the anastomosis in all cases. Splints were not otherwise used routinely. A Foley catheter was left in the bladder and removed after 24 h if there was no immediate function or at 7 to 10 days if there was immediate function (68% of recent transplants). Wound drains were not routinely used.

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Accepted for publication 14 October 1980.

Post-operatively, renal function was monitored clinically and biochemically in all patients. Early in this series, intravenous urography was routinely performed in the second post-transplant week or earlier if indicated (Bewick *et al.*, 1974). Since 1974 this has been superseded by dynamic renal imaging, with computer quantification, with Tc^{99m} DTPA (Hilson *et al.*, 1978). The first study was obtained, in most patients, within 24 h of operation. Subsequent studies were performed on alternate days until discharge from hospital and then when clinically indicated. Thus in most patients a urological complication was diagnosed by a combination of clinical features, deteriorating renal function and in recent years the findings of the Tc^{99m} DTPA scan with supplementary radiographic confirmation where indicated (Burke *et al.*, 1979).

Results

There have been 201 urological complications in 125 transplants in 123 patients. Sixty of these complications (30%) were secondary in that they followed treatment of a previous urological complication. There were 7 recurrent urinary obstructions and 53 secondary or recurrent urinary fistulae. These complications are enumerated in Table 1.

Obstructions

There were 98 obstructive episodes in 75 transplants in 73 patients. Fourteen patients (19%) had died in relation to their obstruction or secondary complications, 10 patients (14%) had died from causes unrelated to their obstruction, 13 patients (18%) were alive on haemodialysis and 36 patients (49%) were alive with functioning grafts 3 months after definite treatment of the obstruction. The incidence and mortality of this complication have declined in the last 3 years from 11.1 to 5.7% and from 30.8 to 12.5% respectively. The causes of obstructive uropathy are listed in Table 2. Forty-eight patients had one primary obstruction in one transplant, 2 patients had one primary obstruction in 2 consecutive transplants, 16 patients had 2 primary obstructions in one transplant (*i.e.* 2 different and unrelated causes of obstruction) and 7 patients had recurrent obstruction in one transplant.

Of the 91 primary obstructions 52 (53%) were due to ureteric stenosis and 11 of the 14 deaths attributable to obstruction were in this category. All 7 recurrent obstructions were in this category. The obstruction was deemed to be a technical fault or due to ureteric necrosis if it occurred within the first post-operative week and due more to chronic ischaemia, possibly as a result of rejection, if it occurred after that time, although there was obviously some overlap. Nineteen of these stenoses (36.5%) developed between 8 and 28 days after transplantation and this subgroup had the highest secondary complication rate (26% mortality; 52% developed urinary fistula; 16% restenosis). All 5 patients who died in relation to

Table 1 Urological Complications of 1000 Renal Transplants

Obstructions
98 obstructions in 75 transplants in 73 patients
Urinary fistulae
93 fistulae in 56 transplants in 56 patients
Primary fistulae 40
Recurrent fistulae 53
  following treatment of a primary fistula 27 in 20 transplants,
  following treatment of a primary obstruction 26 in 16 transplants
*Renal inversion**
7 transplants in 7 patients
Spontaneous rupture
3 transplants in 3 patients
Total
201 urological complications in 125 transplants in 123 patients
Total transplants 1000 in 826 patients

* Is this a complication?

Table 2 Cause of Obstructive Uropathy: 91 Primary Obstructions in 75 Transplants in 73 Patients

Ureteric stenosis		52
Distal third	49	
Middle and distal thirds	1	
Full length	2	
Lymphocele		13
Haematoma		7
Pelviureteric junction obstruction		4
Classical PUJ	3	
Malignant*	1	
Fibrosis around distal extravesical ureter		3
Blood clot in renal pelvis		3
Calculus		2
Malakoplakia†		2
Twisted ureter		1
Haematoma in suburothelial tunnel		1
Round ligament		1
Omental adhesion		1
Malignant deposits in iliac lymph nodes‡		1

* Secondary deposit from primary carcinoma of the bronchus.
† Histological report on one case was not conclusive.
‡ Rhabdomyosarcoma of the adductor muscles of the thigh.

obstruction in this subgroup were noted to have a fresh haematoma in the pelvis at the time of exploration. The worst patient survival was related to those obstructions occurring during the first week (33% mortality; 44% fistula: 11% restenosis) and the worst graft survival was in those who developed obstruction after the first month (8/18 surviving patients lost their graft).

In most instances (46/52 patients—88.5%) the operative technique used to relieve the obstruction was excision of the stenosed segment and ureteric reimplantation either directly into the bladder or into a Boari flap with an 8 FG or 10 FG soft nasogastric tube as a combined ureteric splint and intubated ureterostomy. In only one instance has ureteric meatotomy been tried and this was a failure. In the 5 remaining cases the transplant ureter was too short for reimplantation and so restoration of continuity, after excision of the stenosed segment, was achieved by either anastomosis of the residual ureter or of the renal pelvis to the recipient ureter or by a pyelocystostomy. If the first reoperation was successful in relieving the obstruction and without complication, the patient survival rate with a functioning graft was 62.5%. If a second or third reoperation was required, the survival rates were 41 and 20% respectively. On 4 occasions, either at the first or second reoperation, no ureter remained after excision of the restenosed or fistulous segment and continuity was achieved by interposition of a tailored segment of ileum (ileal chute). In all 4 cases the urinary anastomoses healed but on 2 occasions death resulted from peritonitis as a result of disruption of the enteroanastomosis (one of which was a patient with malignant disease, see below).

In 13 instances ureteric obstruction was due to a lymphocele. Three of these patients also had a distal ureteric stenosis successfully corrected 4 and 6 months previously or 2 years later. The lymphoceles developed 2 to 15 months after transplantation (mean 6 months) and were definitively treated by internal marsupialisation. Two patients died in the early post-operative period from chest infections. The remainder survived with functioning grafts for at least 3 months.

Seven patients developed ureteric obstruction in the early post-transplant period due to the presence of a haematoma. In all cases the haematoma was drained. Of these 7 patients, 5 subsequently developed distal ureteric stenosis and the other 2 developed a further obstruction 2½ and 5 months later due to fibrosis around the extravesical distal ureter which was successfully treated by ureterolysis. One other patient developed the latter complication but without a previously noted haematoma.

Four patients developed pelviureteric junction obstruction. Three occurred in the early post-transplant period and were successfully treated by pyeloplasty. The other occurred at 15 months and was due to a malignant extramural stricture. This was a secondary deposit from a primary carcinoma of the bronchus from which the patient subsequently died (mentioned above). On 3 occasions obstruction was due to a blood clot in the renal pelvis or ureter requiring surgical removal. In one patient this followed renal biopsy and occurred 5 months after a successfully treated ureteric stenosis. The other 2 occurred within 24 h of transplantation and both patients developed ureteric stenosis 2 and 3 weeks later.

Two patients developed calculi. In the first, occurring 10 years after transplantation, ureterolithotomy was successful. In the second, occurring at 18 months, the stone was associated with renal tuberculosis requiring transplant nephrectomy. There was one instance each of a twisted ureter successfully treated by reimplantation, a haematoma in the tunnel of a Politano-Leadbetter ureteroneocystostomy successfully treated by evacuating the haematoma, a kinking of the ureter over the round ligament successfully treated by dividing the round ligament (this woman developed an obstructing lymphocele 8 months later) and a midureteric obstruction due to an omental adhesion successfully treated by ureterolysis.

One patient who developed a rhabdomyosarcoma in the adductor muscles of the thigh subsequently developed ureteric obstruction due to involvement by iliac node deposits.' This boy and the other patient with malignant disease (see above) are classified in this series as dying from their malignancies rather than as deaths due to urological complications. Finally, there were 2 patients who developed obstructions due to malakoplakia, although the histological characteristics in one patient were not conclusive. Both patients had transplant nephrectomy and one died from septicaemia in the post-operative period. The other remains alive and well on haemodialysis 18 months later, having recently received a second, unsuccessful, transplant.

In these 75 transplants as a group no relationship was found between either the incidence of obstruction or the mortality from obstruction and age, sex, length of time on dialysis before transplantation or whether or not there was immediate graft function. However, of the 12 patients who developed obstructions, having received kidneys from living related donors, only 1 patient died (8.3% mortality) compared with 20.6% mortality (13/63 patients) for recipients of cadaveric kidneys. None of the patients receiving "low dose" steroids after a cadaveric graft (15 patients) died as compared with 23.3% mortality (14/60) for patients receiving "high dose" steroids. Although the mortality rate was lower, the incidence of obstruction in the "low steroid" and the live related recipients was the same as in the other recipients.

Urinary Fistulae

There were 93 urinary fistulae in 56 patients (56 recipients). Primary fistulae occurred in 40 patients. Twenty of these patients (50%) developed a total of 27 recurrent fistulae. Sixteen patients who had primary urinary obstructions developed a total of 26 fistulae following surgical correction of their obstruction, which was ureteric stenosis in every instance. Of the 40 recipients with primary fistulae, 13 (32.5%) died as a result of their urological complication(s). Unlike the obstructive uropathies, the annual incidence and mortality from fistulae have remained static.

There was one caliceal fistula due to thrombosis of a lower pole artery and consequent infarction of the lower pole of the kidney. This patient died of septicaemia due to infection in the urine collection that resulted. There were 2 fistulae from the renal pelvis presumed to be due to trauma at the time of donor nephrectomy. Both were successfully closed by suture with an omental patch.

There were 24 primary ureteric fistulae, all from the distal ureter, including disruptions of the ureterovesical anastomosis. As with the obstructive uropathies, fistulae developing within the first week after transplantation were deemed to be technical failures or due to ureteric necrosis, and those after that time to be due to more chronic ischaemia, including rejection. Nine of the 13 deaths from urinary fistulae were in this group. In 8 of these 9 a fresh haematoma in the pelvis was noted at the time of exploration. The highest incidence (50%) of ureteric fistula, as with distal ureteric stenosis, was during the period between the end of the first week and the end of the first month after transplantation (12/24 patients). In most instances, as with ureteric stenosis, the preferred operative technique in patients with a ureteric fistula was excision of the involved segment of ureter and reimplantation either directly into the bladder or into a Boari flap with a ureteric splint/intubated ureterostomy and adequate drainage of the extravesical space. In 5 instances there was insufficient length of ureter for reimplantation and continuity was restored by anastomosis of the transplant ureter or renal pelvis to the recipient ureter or by pyelocystostomy. Only one of these 5 procedures was successful.

As expected, the chances of a patient surviving with a functioning graft fell distinctly (from 36 to 18%) if a recurrent fistula followed surgical treatment. Indeed, of the 5 patients who did survive with a recurrent fistula (11 patients), 2 were treated by transplant nephrectomy and in the other 3 the recurrent fistula was from the bladder.

A primary vesical fistula developed in 13 patients due to disruption of the anterior cystostomy suture line. Small leaks that occurred on removing the urethral catheter and which rapidly resolved on replacing the catheter for a further 2 to 3 weeks, unassociated with further morbidity, are not included. Three patients with a vesical fistula died as a result of their fistula, all with associated intractable urinary infections. One fistula healed with an indwelling urethral catheter for 3 months; the other 12 fistulae required surgical closure. Seven patients developed one or more recurrent vesical fistulae. One of these required transplant nephrectomy for recurrent urinary infections. The other recurrent fistulae were closed successfully. As might be expected, the mortality rate was highest in those patients who developed fistulae in the first week after transplantation despite the presence of a urethral catheter (50% mortality), and in those with recurrent fistulae (43% mortality).

As for the patients with obstructive uropathies, the mortality rate for urinary fistulae was lower in patients receiving grafts from living related donors (28.6% mortality compared with 39.4% for recipients of cadaveric grafts) and in those receiving "low dose" steroids after cadaveric transplantation (27.9% mortality compared with 40.8% for patients receiving "high dose" steroids). The incidence of fistulae in these 2 groups was the same as in other recipients and no other discriminants for incidence of mortality were found.

Spontaneous Rupture

There were 3 instances of this complication, all occurring in the first 8 days after transplantation. Two patients had their grafts removed. The other patient's kidney was repaired and this graft functioned for 2 years before chronic rejection caused a return to haemodialysis.

Renal Inversion

There were 7 instances of renal inversion. In 3 patients this was not recognised until demonstrated on intravenous urography. In the other 4 instances it was recognised at operation after revascularisation. One of these 4 was accidental but the other 3 were inverted because renal perfusion appeared to be better with the kidney in that position. In all 7 instances the subsequent course of the patient could not be attributed to the position of the kidney and so inversion could be regarded as a positional anomaly rather than a complication.

Discussion

The complications presented here are from one of the largest reported single series of renal transplants. There is a significant percentage of "high risk" recipients. Although other individual series have shown a lower incidence of urological complications and a lower mortality (Leary *et al.*, 1975; Salvatierra *et al.*, 1977), reviews with comparable numbers of transplants to our own show similar results to those presented here (Malek *et al.*, 1973; Palmer and Chatterjee, 1978). It should be noted, however, that a significant percentage of transplanted kidneys never function (14% in our series) and are thus unable to develop a urological complication. The incidence of these complications is, therefore, somewhat higher (13.4%) if only functioning grafts are considered.

Obstructive uropathies and urinary fistulae are the main complications, although the distinction between the 2 may be a fine point since ureteric necrosis may present as either, depending on the duration of the necrosis. Although vesicoureteric reflux may be important in a transplant recipient (Urquhart-Hay *et al.*, 1973), we have not routinely looked for it in our patients.

All patient deaths in this series were associated with either obstructive uropathy or urinary fistulae which together accounted for 95% of the complications. Primary obstructions were about twice as common as primary fistulae but the latter carried about twice the mortality rate of the former. Overall, 57 of the 123 patients (46%) were alive with functioning grafts at least 3 months after successful treatment of their urological complication compared with 68% for the 703 patients without urological complications.

The diagnosis of a urological complication is not always straightforward. Urinary fistulae and large intrapelvic collections of urine, blood or lymph may be obvious but obstructions and some ureteric fistulae may be clinically silent. Biochemical tests of renal function may indicate that a problem exists but these tests are non-specific and rejection, in particular, must be distinguished from urological complications as a cause for deterioration in renal function. In our experience the Tc^{99m} DTPA renal scan is the most helpful investigation, particularly in the early case, although recently we have found ultrasound, which is non-invasive, to be a useful diagnostic aid, particularly for obstruction. We have found radiology to be less useful in the early weeks after transplantation because of its dependence on renal function to give delineation of the renal outflow tract

Prevention of complications is of obvious importance and attention to detail in the performance of both the donor nephrectomy and of the transplant itself have been frequently emphasised (Salvatierra *et al.*, 1977) and require no re-emphasis. Similarly, the relationship between the type of ureteroneocystostomy employed and the development of ureteric obstruction has been frequently discussed. We favour the Politano-Leadbetter technique as, in our hands, the Paquin technique has been associated with twice the incidence of obstruction. The extravesical technique of Woodruff should, in theory, have a lower incidence of obstruction, at least for technical reasons but, again in theory, may have a higher incidence of fistula formation, although our data are insufficient for analysis. What perhaps does require emphasis is the potential of prostatic obstruction in causing or exacerbating obstructive uropathy or predisposing to disruption of the bladder closure. Although the numbers are too small for analysis in relative terms, we have felt that attention to this factor has avoided or reduced morbidity in men of the appropriate age in absolute terms.

A final factor in prophylaxis would appear to be the steroid dosage employed. High doses of steroids in this series have been associated with a higher mortality rate in those patients who have developed a complication when compared with patients receiving low dose regimes. This steroid factor may be associated with general nutritional status of the recipients but we have no generally applicable objective parameter for the latter by which to assess this association.

In those patients with established urological problems it is our view that the safest course is early definitive surgical treatment, although some authors have advocated a conservative approach (Desai *et al.*, 1974). Although few reports have commented on the incidence of secondary complications after reoperation (O'Donoghue *et al.*, 1973), this has been a major problem in our experience when the distal ureter has become obstructed or fistulated. Thus we would strongly advocate the use of ureteric splints in reoperations to splint the anastomosis and to provide urine drainage until there is radiological evidence of anastomotic healing and we would also advocate adequate wound drainage during this period. It is possible that a reduction in the dose of immunosuppressive drugs during this period would improve the chances of successful reoperation by allowing better healing. Per-operative biopsy of the kidney may also be of value to help decide how hard one should strive to keep the graft should further problems develop. Finally, we would note that the association of a urological complication with fresh haematoma formation in the second week after transplantation (particularly if urinary tract infection is also present) has been associated with a particularly bad prognosis, and in this type of situation transplant nephrectomy may have been life-saving.

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The Use of the Renal Capsule in Renal and Ureteric Surgery

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Summary—Repair of a large defect of the renal pelvis by a pedicled flap of the renal capsule can be carried out when conventional operative techniques are inapplicable. The renal capsule can also be used to enlarge a stricture or to cover a defect of the proximal ureter.

A renal capsule flap has been used to repair the residual defect after excision of a parapelvic cyst and after a difficult pyelolithotomy (Thompson *et al*., 1963, 1969; Thompson, 1977). It has also been used after wide excision of renal pelvic tumours (Engberg *et al*., 1977) and in a patient with traumatic avulsion of the renal pelvis (Petry, 1974).

We report our experience with this technique in 9 patients treated between 1966 and 1978.

Patients and Methods

The following techniques may be used, according to the extent and location of the lesion:

(1) When replacement of a large defect of the posterior wall of the renal pelvis is required, a triangular flap (6 cm in length) can be obtained from the central portion of the posterior renal capsule. The flap, which has a large renal base, is rotated on itself and sutured to the defect with interrupted sutures of chromic catgut. A nephrostomy tube is left in place for 7 days.

(2) After total excision of the renal pelvis a new collecting system can be constructed by means of a combined anterior and posterior capsular flap (Fig. 1). The flaps are folded down from the kidney, rotated on themselves and sutured together with interrupted sutures of 4/0 or 5/0 chromic catgut. An elliptical opening is left at the dependent portion of the new pelvis and sutured to the spatulated ureter. A nephrostomy is routinely used, together with a splint catheter in the "capsule pyeloplasty" and the upper ureter.

(3) In the management of extensive upper ureteric stenoses, a long capsular flap can be obtained from the lower pole of the kidney (Fig. 2). It should be large and its length tailored to the length of the ureteric lesion. The ureterotomy should be extended 1 cm into healthy ureteric tissue and the capsular flap sutured to the borders of the ureterotomy. A splint is left in place for one week.

In our series of 9 patients there were 3 main indications for the use of a capsular flap:

(1) Complications due to difficult renal stone extraction. In 3 cases of staghorn calculi the posterior wall of the renal pelvis was damaged during the operative procedure. In 2 instances of large pelvic stones the intrarenal pelvis and the pelviureteric junction were injured.

(2) Ureteric strictures following ureterotomy for recurrent calculi (3 cases).

(3) Reconstruction of the renal pelvis following excision of the pelvis for transitional cell tumour (one case).

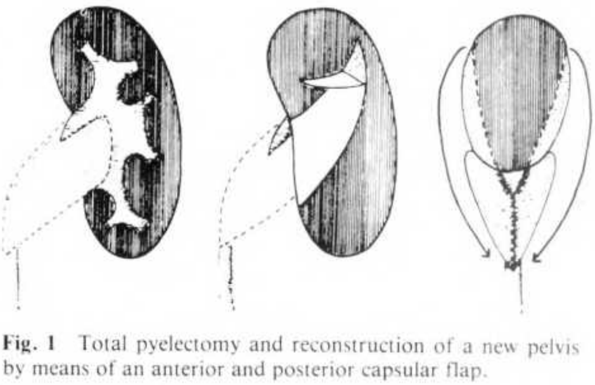
Fig. 1 Total pyelectomy and reconstruction of a new pelvis by means of an anterior and posterior capsular flap.

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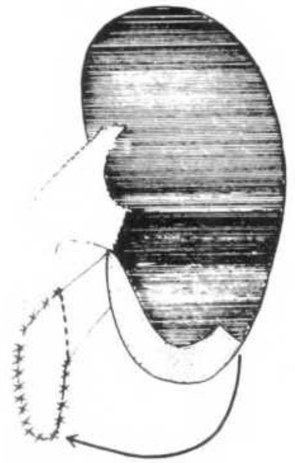

Fig. 2 Use of a long capsular flap from the lower pole to enlarge a stricture of the proximal ureter.

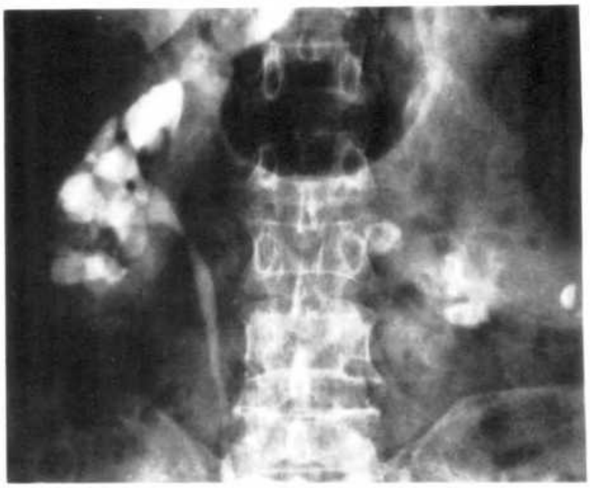

Fig. 3 Intravenous urogram 2 years before the appearance of the renal pelvic tumour. Left pyonephrotic kidney with calculi. Right pyelonephritic kidney with normal renal pelvis.

Results

The pedicle graft of renal capsule has given good results in the 8 cases of lithotomy complications. Intravenous urography showed a normal pelviureteric junction without residual obstruction during regular and diuresis urography.

Long-term radiological follow-up was maintained in several instances (mean follow-up 6.5 years; longest follow-up 12 years).

Renal function estimated by DMSA showed post-operative values to be unchanged.

Urine cultures remained sterile except in one case where urinary tract infection persisted for 7 months.

The following patient, who underwent total reconstruction of the renal pelvis, had satisfactory renal function:

This 72-year-old female, a chronic phenacetin abuser for 14 years, underwent left nephrectomy for calculus pyonephrosis (Fig. 3). Two years later she was admitted as an emergency because of renal insufficiency. Serum creatinine was 6 mg%. The retrograde pyelogram showed a large tumour involving the pelvis and upper ureter and causing considerable caliectasis (Fig. 4). The pelvis and upper ureter were completely excised and a new pelvis constructed using the capsular flap technique (Fig. 1). Histological examination showed an infiltrating transitional cell carcinoma of the renal pelvis.

A post-operative nephrogram demonstrated the new pelvis and good drainage to the ureter (Fig. 4). Renal function remained stable (serum creatinine 3 to 3.5 mg%) until the patient's death 11 months later from widespread metastases.

Discussion

Total or partial reconstruction of the renal pelvis using the renal capsule is easily performed and gives excellent long-term results.

Use of the capsular flap has been studied histologically in the dog (Thompson *et al.*, 1963) and it was found that after 2 to 3 weeks there was

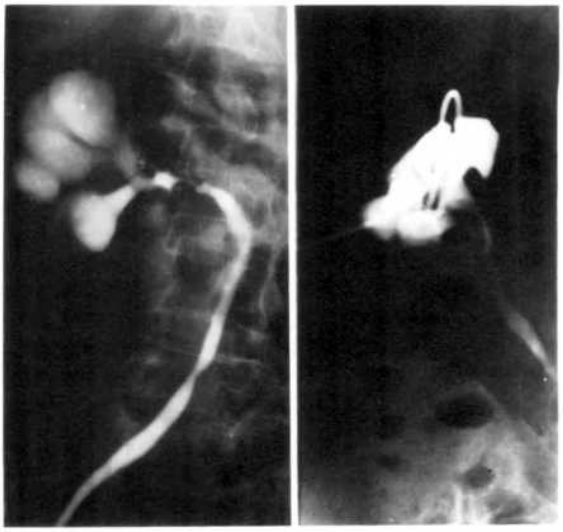

Fig. 4 Retrograde pyelogram: large pelvic tumour with caliectasis. Post-operative nephrogram: new capsular pyeloplasty.

complete re-epithelialisation of the flap, originating from the urothelium. There was no muscular regeneration even after one year.

In the animal model, calcification of the flap as well as calculus formation can occur. In one patient reported by Thompson (1977), removal of a staghorn calculus was followed by the development of a linear calcification on the serosal margin of the repaired upper ureter. This did not occur in our patients.

The renal capsular flap appears to be an excellent substitute for renal pelvis and ureter. Its good vascular supply favours the construction of a new renal pelvis (this would not be the case with a free graft of peritoneum) and, in cases of upper ureteric strictures, the post-operative period is shorter than that which follows Davis's intubated ureterotomy.

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Renal Angiomyolipoma: A Review of the Literature and a Report of 4 Cases

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Summary—Four cases of renal angiomyolipoma are presented in patients with no other stigmata of tuberous sclerosis. The presentation, radiological and pathological features are reviewed.

Angiomyolipomas are either benign tumours or hamartomatous lesions, containing tissues normally present in the organ but abnormal in their arrangement, quantity and degree of maturation. As the name suggests, the tumour is composed of variable mixtures of smooth muscle, blood vessels and fat. There is controversy as to whether they are developmental anomalies or true neoplasms.

Two distinct types of renal angiomyolipoma have been noted. The first is found in patients with tuberous sclerosis, occurring in 40 to 80% of cases (Lynne *et al.*, 1979). These tumours are usually small, asymptomatic, bilateral and often found only at autopsy. The second type occurs rarely amongst the general population, some 200 cases having been reported to date (Busch *et al.*, 1976). They usually present as large, unilateral, symptomatic renal masses. This type is totally independent of the tuberous sclerosis complex but is histologically indistinguishable from the first type. It is frequently associated with intrarenal or retroperitoneal haemorrhage because of its vascular nature, the resultant pain and/or mass prompting the patient to seek medical attention. It can masquerade as several other renal lesions (McCullough *et al.*, 1971); in fact, in 150 cases seen before 1964, none was diagnosed correctly prior to surgery (Vasko *et al.*, 1965).

Four cases of isolated renal angiomyolipoma are reported which demonstrate the differing modes of presentation. None of the cases had any of the stigmata of tuberous sclerosis.

Patients

Case 1. A.S., a 63-year-old woman, presented in 1969 with a right axillary mass. Excision biopsy of the mass showed poorly differentiated carcinoma compatible with an origin in breast or kidney, though no breast lump was palpable. An intravenous urogram revealed the lower pole of the right kidney to be displaced laterally with compression of the inferior calices, the appearances suggesting a lower polar tumour.

At surgical exploration a large pale yellow lower pole tumour measuring 80 × 80 × 45 mm was noted and a radical nephrectomy performed. No lymph node involvement was noted. Histological examination revealed the tumour to consist of fat cells, fibrous tissue, smooth muscle elements and atypical blood vessels. The artery-like vessels were ensheathed in smooth muscle with no true elastic laminae present. The diagnosis of angiomyolipoma was made.

The patient was lost to follow-up for 6 years but was seen again in August 1975 with recurrence of her right axillary mass. Excision biopsy revealed metastatic carcinoma, probably from a breast origin. Bone scan revealed extensive metastatic carcinoma. The patient was treated with radiotherapy and cytotoxic therapy but failed to respond and died in July 1976. The primary carcinoma was not identified.

Case 2. N.F., a 52-year-old woman, was admitted in August 1977 with a 6-month history of weight loss, tiredness and fainting. Prior to admission the patient developed severe constant left iliac fossa pain, nausea and vomiting. Physical examination revealed hypotension, anaemia and a tender mass extending from her left loin to the left iliac fossa. Haemoglobin on admission was 7 g%; urea and electrolytes were normal. Plain abdominal films suggested a left retroperitoneal haematoma with lateral displacement of the left kidney. The patient was transfused 6 units of blood, her haemoglobin rising to 9.6 g%. The following day, marked guarding in her left iliac fossa was present with abdominal distension. The patient was transfused a further 6 units of blood, her haemoglobin rising to 12.1 g%. An

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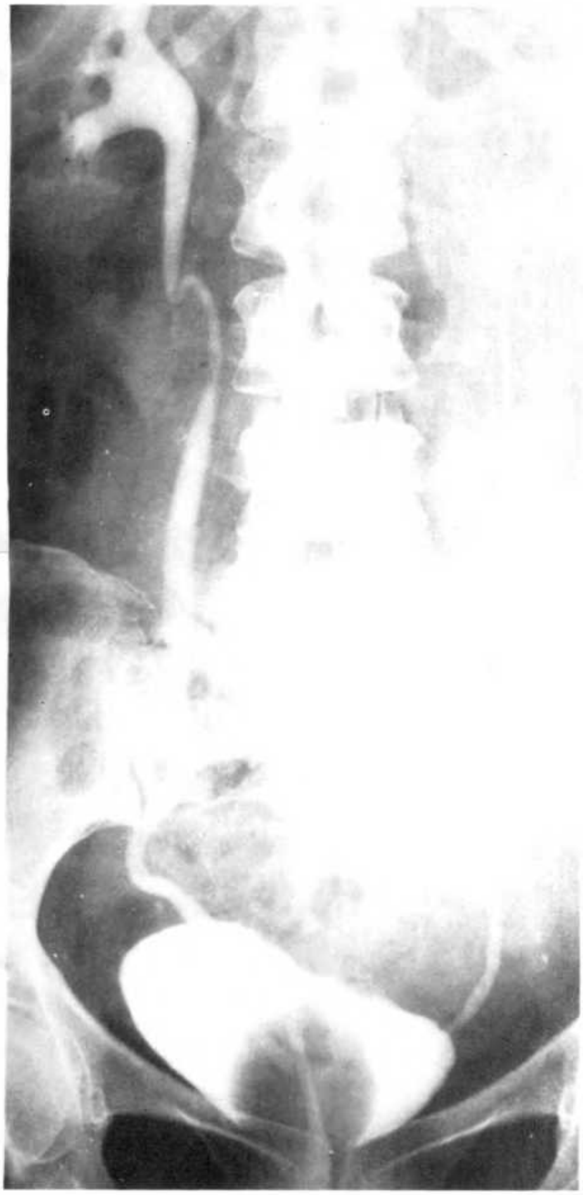

Fig. 1 Intravenous urogram showing loss of the left psoas shadow due to retroperitoneal haematoma with stretching of the left ureter.

intravenous urogram showed a normal right kidney; the left kidney was displaced laterally, with stretching of the left ureter (Fig. 1). At surgical exploration a large retroperitoneal haematoma was evacuated, revealing a fleshy tumour in the lower pole of the left kidney measuring 50 × 40 × 10 mm. A left nephrectomy was performed, no lymph node involvement being noted. Histological examination of the tumour revealed an angiomyolipoma, large areas of haemorrhage, necrosis and inflammation being noted in the tumour. The patient has remained well to date.

Case 3. E.A., a 65-year-old woman, was referred to the Gynaecology Department in December 1978 with a 2½-year history of intermittent post-menopausal vaginal bleeding, recent onset of low back pain and bilateral ankle oedema. Physical examination revealed a lower abdominal mass arising in the pelvis, an enlarged nodular liver with ascites, severe sacral and leg oedema, and bilateral basal crepitations. Vaginal examination revealed a bulky uterus with nodules in the vaginal wall. The patient was urgently admitted for investigation but shortly after admission suffered a left pulmonary embolism. Over the ensuing 10 days she steadily deteriorated, finally succumbing 2 weeks after admission. An autopsy confirmed the clinical impression of a primary carcinoma of cervix with widespread carcinomatosis and a left pulmonary embolus. A 10 mm diameter tumour was present in her left kidney and histologically was an angiomyolipoma.

Case 4. D.H., a 57-year-old woman, was seen in October 1979 after the sudden onset of severe right loin pain, nausea and vomiting, persisting for 5 days with a

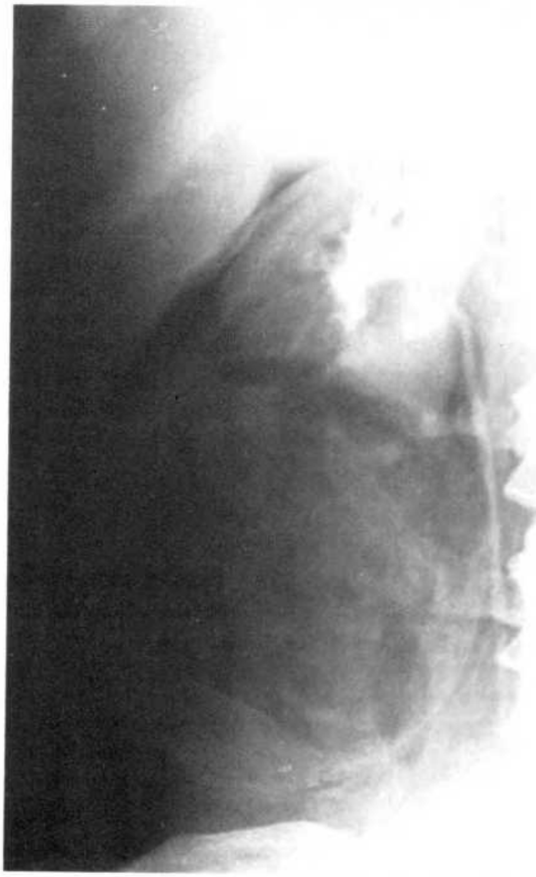

Fig. 2 Intravenous urogram showing a well demarcated radiolucent tumour at the lower pole of the right kidney with distortion of the lower pole calices.

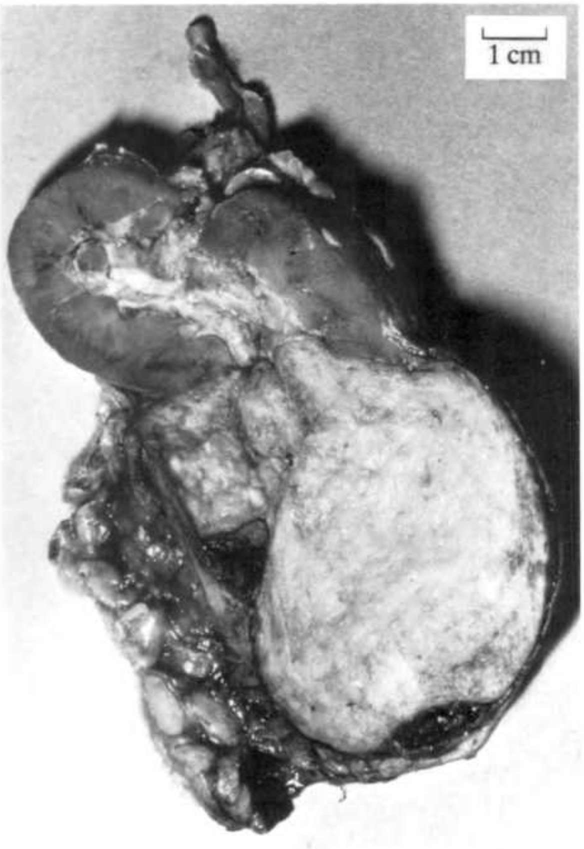

Fig. 3 Photograph of an 80 mm diameter tumour at the lower pole of the right kidney.

pyrexia 3 weeks previously. She continued to have right loin discomfort until seen. Physical examination revealed a tender enlarged right renal mass. An intravenous urogram revealed a well demarcated radiolucent tumour at the lower pole of the right kidney with distortion and irregularity of the lower pole calices (Fig. 2). The left kidney was normal. Ultrasound examination of the mass showed it to be poorly transonic and containing numerous echoes. At operative exploration a large tumour measuring 80 × 80 × 60 mm was present at the lower pole of the right kidney, partially occluding the second part of the duodenum by pressure (Fig. 3). A right nephrectomy was performed; no lymph node involvement was noted. Macroscopically the tumour was uniform, yellow in colour and clearly demarcated from the normal renal tissue. An area of recent haemorrhage was noted in the tumour and histological examination showed an angiomyolipoma. The patient is well at present.

Discussion

There are, at present, 200 reported cases of renal angiomyolipoma not associated with tuberous sclerosis. Renal involvement in these cases is usually unilateral, solitary and the female to male ratio is 4 to 1 (Kavaney and Fielding, 1975), with the usual age at detection being between 40 and 60 years (Allen and Risk, 1965), and our cases fit closely into this pattern.

The symptoms of renal angiomyolipoma usually occur from haemorrhage into or from the tumour, causing flank pain, hypovolaemic shock, an enlarging mass, haematuria, gastrointestinal symptoms or mild to acute abdominal pain. Several series combined together have shown that, at presentation, 87% had pain, 47% a palpable mass and 40% haematuria (Allen and Risk, 1965; Price and Mostofi, 1965; Hajdu and Foote, 1969; McCullough *et al.*, 1971).

Case 2 presented with many of the classical symptoms of hypotension, flank and abdominal pain, and a palpable mass. Case 4 presented similarly with flank pain and pyrexia, the pyrexia due probably to the effects of tumour necrosis.

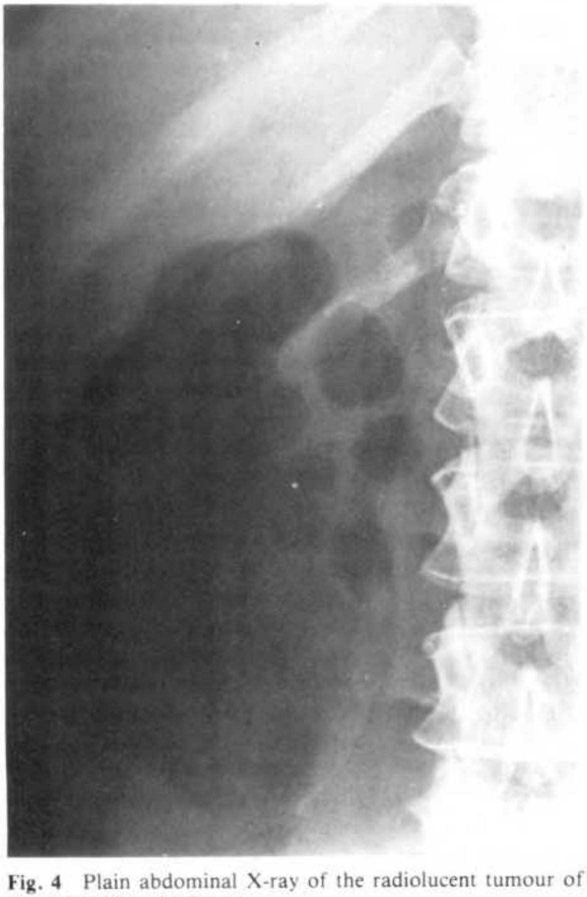

Fig. 4 Plain abdominal X-ray of the radiolucent tumour of the right kidney in Case 4.

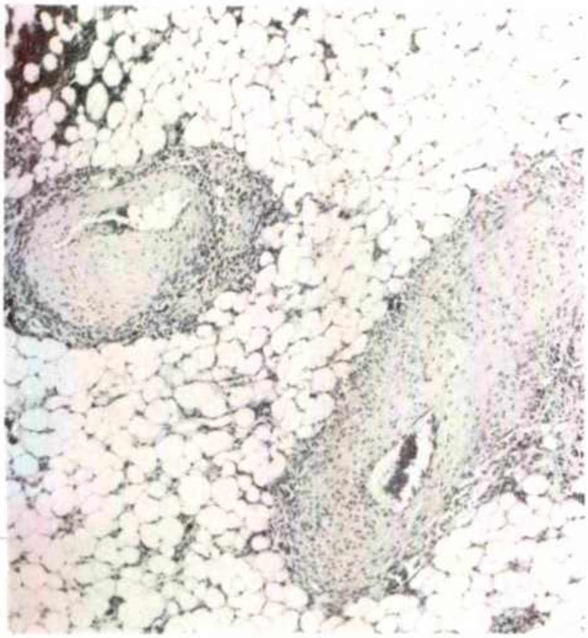

Fig. 5 Abnormally thickened blood vessels present in a fatty stroma (H and E ×44).

Cases 1 and 3 were asymptomatic and the renal lesions were only incidental findings. This is in keeping with the observations of Perou and Gray (1960), who recorded 44 out of 52 cases to be asymptomatic.

The radiological features of angiomyolipoma can be confusing, resulting in the misdiagnosis of polycystic disease or renal carcinoma (Khilnani and Wolf, 1961; Love and Frank, 1965; Viamonte *et al.*, 1966; Green, 1968; Seshanarayana and Keats, 1968; Chonko *et al.*, 1974). In fact, of the 150 cases seen before 1964, none was diagnosed correctly pre-operatively. The lesions frequently appear radiolucent because of their fat content (Fig. 4). Haemorrhage into the lesion or perinephric areas may obscure the lucency, but nephrotomograms may help in this respect. On intravenous urography, stretching and distortion of the caliceal systems by the mass may be noted, as in Figure 2 (Chonko *et al.*, 1974).

The characteristic angiographic findings include hypervascularity with abnormal vessel distribution, branching patterns, unusual arterial vessel tortuosity, pooling of opaque contrast in ectatic vessels, engorged venous channels and lack of normal vascular contour with tapering (Hartveit and Halleraker, 1960; Perou and Gray, 1960; Khilnani and Wolf, 1961; Viamonte *et al.*, 1966). However, this hypervascular pattern of tumour neovascularity is also consistent with renal malignancies, particularly carcinoma, and it may not be possible to distinguish it clearly from the carcinoma by angiography if the tumour is a solitary one. Some cases with both types of tumour coexisting in the same kidney are reported in the literature (Kavaney and Fielding, 1975; Lynne *et al.*, 1979). However, Viamonte *et al.* (1966) and Camacho *et al.* (1979) have reported the presence of well developed, discrete interlobular and intralobular arterial aneurysms which are characteristic of angiomyolipoma, although renal carcinomas may sometimes show bizarre and random aneurysmal dilatations of non-specific tumour vessels.

The gross appearance of renal angiomyolipoma depends on the predominant cell type, being yellow, grey or beefy-red in colour, depending on the proportion of fat to smooth muscle cells (Price and Mostofi, 1965). Repeated sectioning may be required to demonstrate the true nature of the lesion, since the proportions of the 3 basic elements may vary considerably. The tumour may have an angiomatous appearance and haemorrhage and/or necrosis may be present, making gross differentiation from a renal carcinoma difficult (Farrow *et al.*, 1968).

Histologically the tumour is composed of 3 distinct elements: adult fat cells, smooth muscle and atypical blood vessels. The abnormal blood

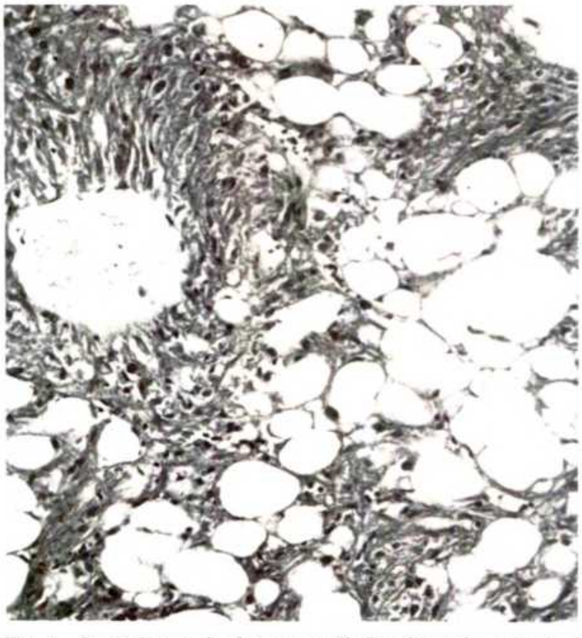

Fig. 6 Smooth muscle elements radiating from the abnormal vessels into the surrounding fat (H and E ×125).

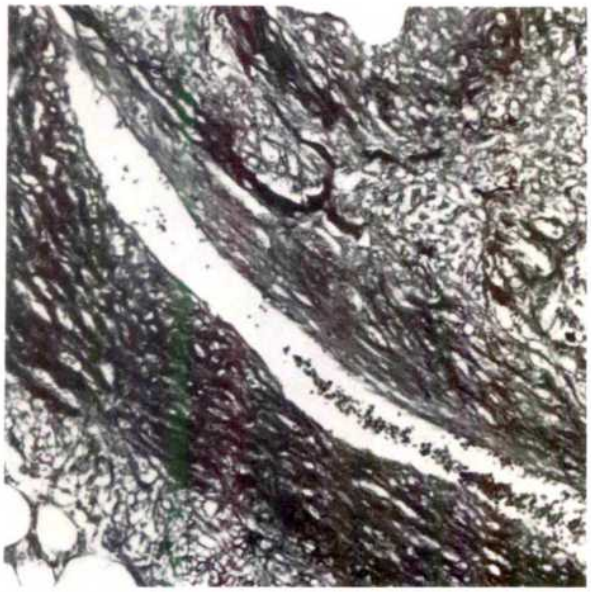

Fig. 7 Blood vessels with fragmented irregular elastic fibres (Weigert's elastic stain (Miller's modification) × 125).

vessels with markedly thickened walls are present in the predominantly fatty stroma (Fig. 5) and strands of smooth muscle may be seen to radiate from these abnormal vessels into the surrounding fat, forming sheets of cells (Fig. 6). A fibrous tissue component may also be seen. Considerable amounts of stainable, elastic tissue may be present, particularly in the adventitia of the vessel walls, although a complete internal elastic lamina is absent (Fig. 7). In our cases, these abnormal vessels contained many fine irregular elastic fibres and this is in agreement with the findings of Hartveit and Halleraker (1960) and Perou and Gray (1960). However, these findings are at variance with those of Tweeddale *et al.* (1955), who used the less sensitive stain of Verhoeff rather than the Weigert's and Orcein stain which we have used.

No discernible histological differences were noted between the tumours in patients with or without tuberous sclerosis. These tumours were frequently misdiagnosed as sarcomas, usually liposarcoma (Price and Mostofi, 1965).

Regional lymph node involvement has been noted in several cases, but the evidence suggests that nodal involvement represents the multicentric origin of the angiomyolipoma (Busch *et al.*, 1976). This is supported by the finding of 2 cases of renal angiomyolipomata in association with pulmonary lymphangiomyomatosis (Corrin *et al.*, 1975).

The differential diagnosis of renal angiomyolipoma, with or without tuberous sclerosis, includes renal neoplasm or polycystic disease of the kidney. If the stigmata of tuberous sclerosis are present, the diagnosis is still difficult, since all 3 lesions may be present within the same kidney. In unilateral lesions without the stigmata of tuberous sclerosis, differentiation from a renal neoplasm may be impossible when the classical triad of painless haematuria, flank pain and a palpable mass are present.

Finally, the diagnosis should be borne in mind by all surgeons, since 25% of patients with renal angiomyolipoma described in the literature presented with severe abdominal pain and/or shock, which necessitated emergency laparotomy and resultant nephrectomy. Massive perirenal haemorrhage has been the most consistent finding in these cases, though usually there has been a history of intermittent abdominal or flank pain indicative of previous episodes of haemorrhage (Burkitt, 1948; Herman, 1948; MacDougall, 1960).

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Chronic Peripelvic Extravasation Treated Conservatively

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Summary—Three cases of chronic extravasation of urine secondary to ureteric stone are described. All were successfully treated conservatively and resolution was complete. The clinical features are more important than the urographic appearances in managing these cases and surgery may not be necessary.

A urinoma is an encapsulated collection of extravasated urine; early diagnosis is important for successful treatment (McInerney *et al.*, 1977). Of their 5 cases 3 required nephrectomy.

Smulewicz *et al.* (1970) also reported spontaneous rupture of the renal pelvis to be a serious condition leading to urinoma and perinephric infection severe enough to result in nephrectomy.

We report 3 cases of extravasation secondary to stone treated conservatively without sequelae.

Patients and Methods

Case 1. (Fig. 1) A 45-year-old man had had 4 days' intermittent colicky right-sided loin pain radiating to his testicle. Urography showed a normal nephrogram and normal calices with extravasation on the 5-min film. The extravasation gave the appearance of a double ureter and it appeared to be coming from the renal pelvis. Later it spread around the kidney. There was a stone at the level of the third lumbar vertebra. Cystoscopy 2 days later showed one ureteric orifice on each side of the bladder. The following day he passed a stone. Urography was normal 2 weeks later.

Case 2. This 52-year-old man presented with 14 days' backache and 6 days' dull ache in the right loin which had moved to the groin by the time of admission. On examination he was tender with guarding in the right iliac fossa. He had 2% glycosuria; blood urea was 9.2 mmol/l, blood sugar was 10.9 mmol/l and he was pyrexial. He was initially thought to have pneumonia and intestinal obstruction but chest and abdominal X-rays were normal. The possibility of a perinephric abscess was considered.

The nephrogram was normal and on the 5-min film extravasation was seen to arise from the pelviureteric junction region (Fig. 2a) and later surrounding the kidney (Fig. 2b). The ureter was outlined as far as a stone. The patient was treated conservatively while his diabetes was brought under control. Cystoscopy was performed 5 days after admission and Dormia extrac-

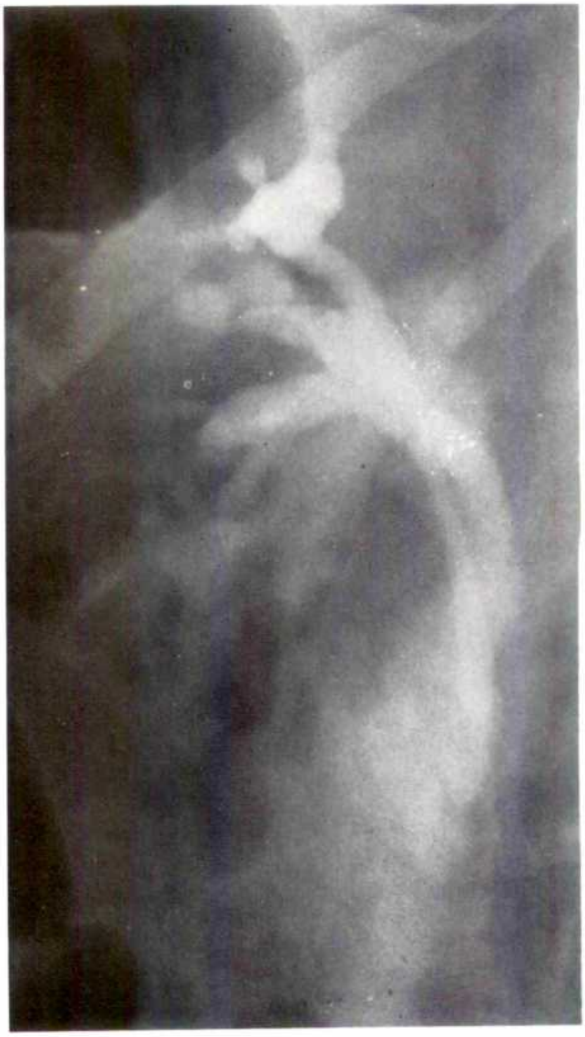

Fig. 1 Extravasation established before the examination. Contrast leaking from the renal pelvis.

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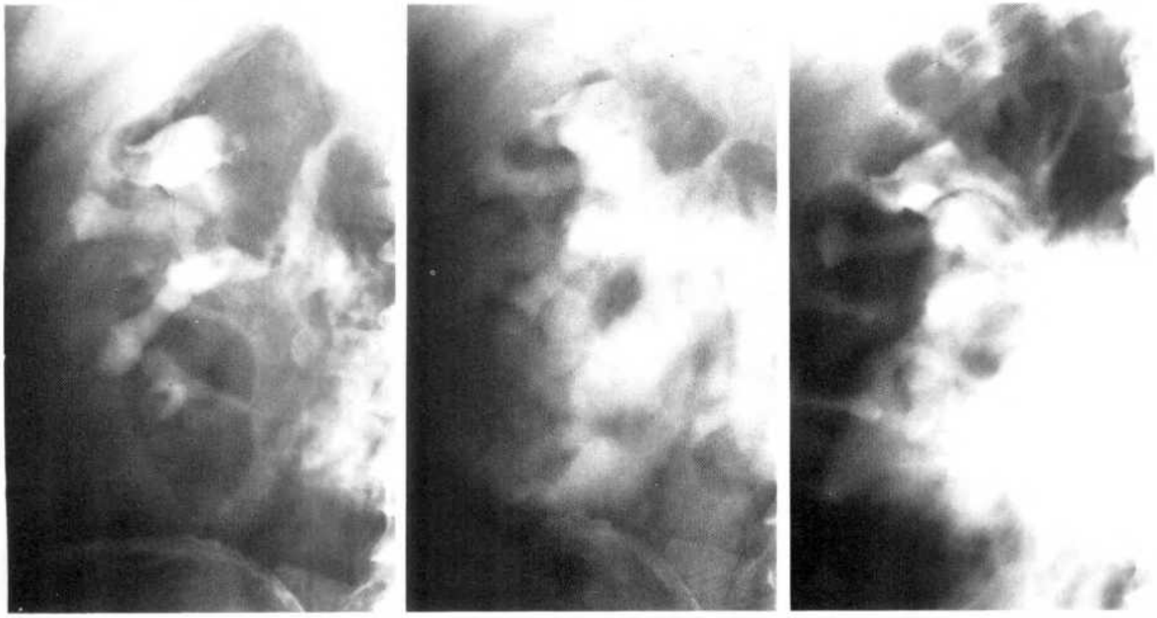

Fig. 2 Extravasation established before the examination. (a) Contrast leaking from the renal pelvis on the 5-min film. (b) The large cavity seen on a 1-h film. (c) A 30-min film from an examination 8 days later shows the cavity persisting.

tion of the stone was unsuccessful. Urography 8 days later showed appearances similar to those on the first occasion but the extravasation now appeared to be within a closed cavity (Fig. 2c). The patient's symptoms gradually settled and the stone was passed. Urography 6 weeks later was normal.

Case 3. This 39-year-old man complained of pain in the right lower lumbar region radiating to the right groin. He had vomited twice. There was no previous history. He was distressed with guarding in the right loin and was tender in the right renal angle. The initial nephrogram on the right was less dense than the left kidney. On the 5-min film the nephrogram was denser and the calices had appeared. On the 15-min film there was extravasation from a fornix and the ureter was seen (Fig. 3a).

The patient continued to have pain and abdominal distension. Urography 12 days later showed a normal nephrogram at 1 min, extravasation in the 5-min film (Fig. 3b) and on the 20-min film extension of the extravasation into a closed cavity (Fig. 3c). He passed a 3 mm diameter stone 4 days later and urography 6 weeks later was normal (Fig. 3d).

Discussion

It is accepted that forniceal backflow is of no significance, having no sequelae and being a natural path for decompression of the pelvicaliceal system (Hinman, 1961; Caro and Waldbaum, 1976). On the other hand, spontaneous rupture of the pelvis has been reported to be a serious condition requiring nephrectomy (Smulewicz *et al.*, 1970; Trapnell, 1969; Davidson, 1971). None of our patients needed surgical intervention despite the fact that one of them was a pyrexial diabetic at the time of extravasation, similar to one of Trapnell's patients who required nephrectomy (Trapnell, 1969). These cases of spontaneous rupture must be distinguished from erosion of the pelvis or ureter at the site of a stone (Eaton and Martin, 1981).

In the 2 cases with extravasation seen on more than one film, one had extravasation from the pelvis and one from the fornices, suggesting that either site can give rise to a urinoma or pararenal pseudocyst under appropriate conditions.

We believe that the mere demonstration of a urinoma at urography need not imply the necessity for early operation on the kidney and that advice on surgery must depend on the clinical features of the case. Careful observation is, of course, very important and the patient should remain in hospital until the stone is passed or removed. Once the obstruction is relieved the leak will be sealed off and the urinoma can resolve.

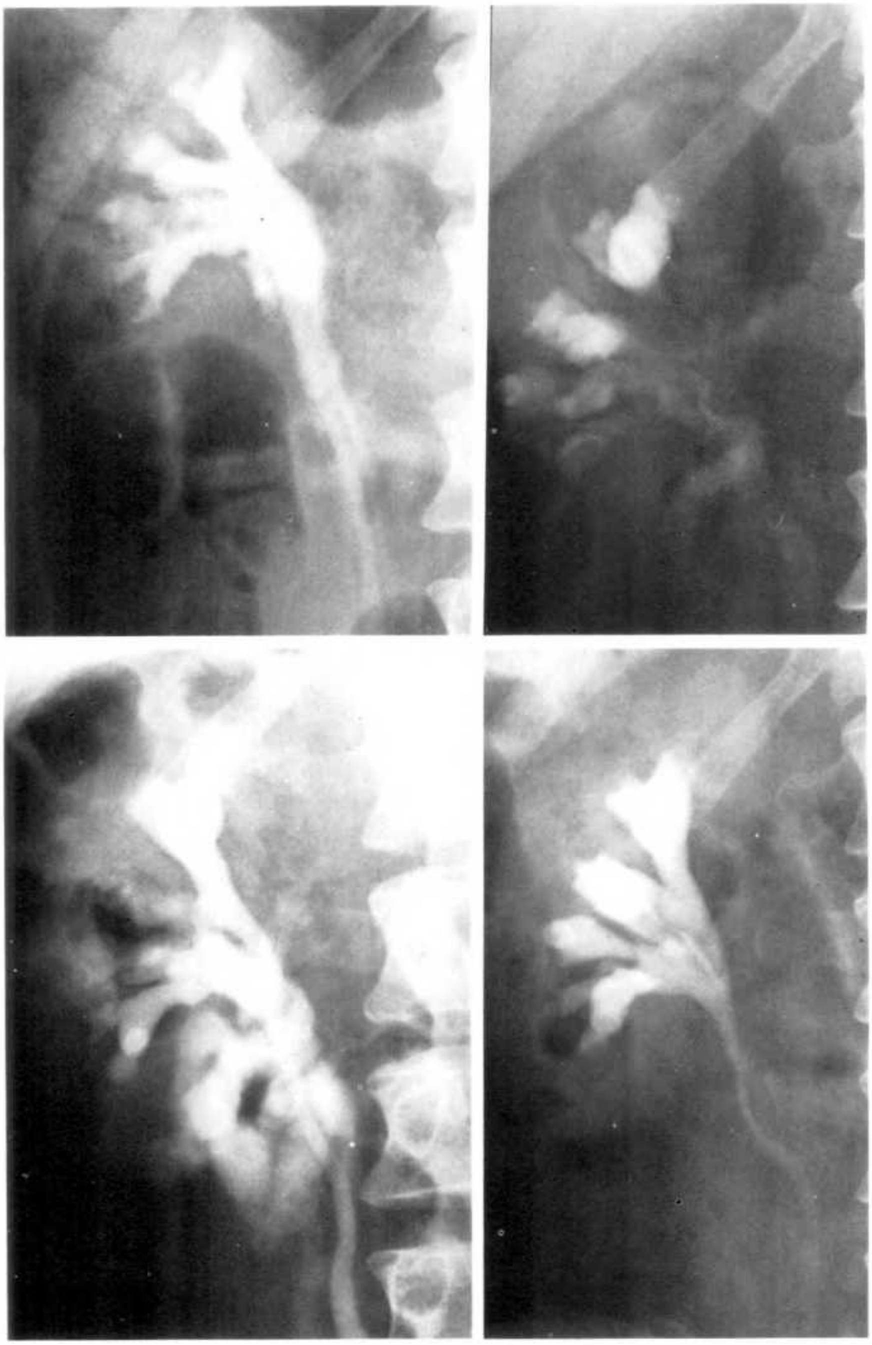

Fig. 3 (a) Initial examination. At 15 min extravasation can be seen from the middle group of calices spreading around the ureter. The nephrogram is no longer dense. (b) Twelve days later the 5-min film shows extravasation from the middle group of calices. (c) The same examination at 20 min: a closed cavity is outlined. (d) Six weeks later. Normal urography at 15 min.

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A Control Study of Dietary Factors in Renal Stone Formation

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Summary—Fifty-one first admission renal stone patients and an equal number of controls were interviewed and a dietary history of the average weekly intake was collected from each participant.

A comparison of the dietary intake per kilogram body weight in each group was made using standard statistical procedures. None of the nutrient intakes showed a significant difference, but dietary fibre intake and the percentage of energy provided by carbohydrate were consistently higher in the control group, whereas the percentage of energy provided by fat was consistently higher in the renal stone group.

Renal stone is a condition affecting about 8% of the Irish population at some time in their lives. There are many types of stone and great variations in the incidence of each type. Calcium oxalate stones account for 50 to 80% of all renal stones, calcium phosphate stones for some 20% and mixed stones for approximately 10%. Uric acid, cystine, xanthine and oxalate stones account for approximately 5% (*British Medical Journal*, 1977). The cause varies with the type of stone, but the precise cause can be identified in only about 15% of Irish patients. Many metabolic causes, dietary factors and indirect, non-dietary factors have been identified (Dent, 1976).

The following dietary elements have been identified as contributors to stone formation: fluids, carbohydrate (Suzuki, 1934; Irving, 1973); animal protein (Robertson *et al.*, 1978); fats, lysine, arginine (Irving, 1973); refined sugar (Haglett and Herman, 1973; Gibbon, 1975); fibre (Zarembski and Hodgkinson, 1969; Gibbon, 1975, 1978 (personal communication)); calcium (Campbell and Harrison, 1970); phosphate (Campbell and Harrison, 1970; Irving, 1973); zinc, aluminium, iron, copper (Campbell and Harrison, 1970); sulphur (Haglett and Herman, 1973); magnesium (MacIntyre *et al.*, 1963; Campbell and Harrison, 1970); vitamin A (*British Medical Journal*, 1977); thiamine (Gershoff, 1964; Haglett and Herman, 1973; Hodgkinson, 1977); vitamin B6 (Campbell and Harrison, 1970; Haglett and Herman, 1973; Hodgkinson, 1977; Robertson *et al.*, 1978); folic acid (Davidson *et al.*, 1973; Haglett and Herman, 1973); vitamin C (Hatch *et al.*, 1980); vitamin D (Haglett and Herman, 1973; Irving, 1973); phytic acid (Gibbon, 1975); oxalate (Archer *et al.*, 1957; Zarembski and Hodgkinson, 1963; Haglett and Herman, 1973; *British Medical Journal*, 1977; Hodgkinson, 1977, 1978); purine (Davidson *et al.*, 1973; Haglett and Herman, 1973; Dent, 1976).

Indirect non-dietary factors include climate, sunshine and humidity (Haglett and Herman, 1973).

It was decided to conduct a case-control dietary study on renal stone patients to determine if there was any association between dietary components and renal stone formation in Ireland. The study was carried out for 24 weeks from January to June 1978. During this time 51 renal stone patients and 51 suitably matched controls were interviewed in respect of diet and diet-related characteristics. The nutrient content of the diets of the 2 groups was analysed and compared using standard statistical methods.

An average daily intake was taken as one-seventh of the weekly intake and this was analysed for its content of 30 dietary variables, which were as follows: energy, protein, fat, carbohydrate, percentage of energy from protein, percentage of energy from carbohydrate, percentage of energy from fat, sucrose, cellulose, lignin, non-cellulose polysaccharide, total fibre, alcohol, vitamin A, thiamine, niacin, riboflavin, vitamin B6, folic acid, vitamin C, calcium, phosphate, iron, magnesium, sulphur, sodium, potassium, water, oxalate, purine, nitrogen.

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Patients and Methods

The study sample consisted of all first admission renal stone patients (RS) in the Meath Hospital Urological Unit during the period of the study.

Urine analysis in the study group showed 9 patients with hypercalciuria, 3 with hyperoxaluria and 2 with a trace of cystinurea. Serum analysis revealed 2 patients with hyperuricaemia but no other urinary or serum abnormalities were noted. Of 19 renal stones analysed, 10 (52%) contained calcium oxalate as the major constituent, 8 (42%) contained calcium phosphate as the major constituent and one contained mainly protein. The other stones did not pass and were not surgically removed.

The control sample included patients of the Urological Unit under observation or treatment for conditions which did not involve dietary problems (*e.g.* obese and underweight patients) or dietary treatment. Having satisfied this requirement, each control patient (C) was matched with case by age, sex and area of residence (rural or urban).

Diet History Methodology

The interviews included a full dietary history of an average weekly intake using a standardised questionnaire. This was based on the typical pattern for 24 h, incorporating a frequency column of how often the pattern or food type occurred on a weekly basis. The average daily intake, derived from weekly totals, was then estimated and expressed in terms of nutrients per kilogram of body weight per day. These data provided the basis for subsequent analysis of the differences between cases and controls. Those interviewed were asked to describe the food consumed in standard household measurements, or, if possible, exact weights which were converted into grams using standard conversion data of household measures to gram weight.

The questionnaire also included sections for information on the following:

(*a*) Frequency of eating high risk foods, *i.e.* foods containing large amounts of specific food factors that have been associated with renal stone formation in past research: purines, vitamin D and calcium.

(*b*) Anthropometry.

(*c*) Regular intake of drugs or dietary supplements.

(*d*) Smoking habits.

(*e*) Occupation and activity rating.

(*f*) Vacations or assignments away from home in past 5 years (climate changes).

Analysis of Data

The energy and nutrient content of 813 foods was stored on tape for computer analysis of the diets. Food composition data were taken from 3 sources, for macronutrients, vitamins and minerals (McCance and Widdowson, 1967), oxalate food values (Zarembski and Hodgkinson, 1962) and dietary fibre (Southgate *et al.*, 1976).

Each diet was analysed for content of the following nutrients or food factors: energy, protein, fat, alcohol, cellulose, non-cellulose polysaccaride, lignin, total dietary fibre, percentage of energy supplied by protein, fat, carbohydrate, vitamin A, thiamine, niacin, riboflavin, vitamin B6, folic acid, vitamin C, calcium, phosphorus, iron, magnesium, sodium, potassium, sulphur, sucrose, purine nitrogen, fluid and oxalate.

The results in nutrients per kilogram of body weight were then compared using standard statistical procedures.

Statistical Analysis

A statistical analysis of the dietary intake was undertaken to establish if there was any significant difference between the intake of the 2 groups with respect to each of the 30 nutrients investigated. This analysis included the calculation of averages and standard deviations for each nutrient, the paired t-test for differences between correlated pairs of means (Guildford, 1973) and the Kolmogorov-Smirnov test for comparing a series of frequencies in 2 distributions. It has recently been argued that a high fibre intake may be beneficial in the control of kidney stone formation (Zarembski and Hodgkinson, 1969; Gibbon, 1975, 1978 (personal communication)), which implies that a chi-squared "goodness of fit" calculated from a one-tailed Kolmogorov-Smirnov statistic (Lindgren, 1976) would be quite appropriate for the various fibre intakes. Chi-squares were similarly calculated for calcium, purine nitrogen, water, folic acid and percentage of energy intakes.

Results

The average daily intakes, standard deviations and the variation in the averages are listed in the Table. In addition to the values of the t-ratios,

Table Comparison of Average Daily Intake Levels Between Renal Stone Patients and Controls per Kilogram of Body Weight

Nutrients and food factors	*(A) Renal stone patients*		*(B) Control patients*		*Differences*	*Significance*		
	$\bar{x}$	*sd*	$\bar{x}$	*sd*	*(A-B)*	*t*	*d*	x^2
Energy	50.73 kc	16.54	50.70 kc	17.48	0.03	0.01	0.06	
Protein	1.57 g	0.46	1.65 g	0.50	−0.08	−0.82	0.08	
Fat	2.48 g	0.90	2.43 g	1.02	0.05	0.31	0.08	
Carbohydrate	5.08 g	1.94	5.22 g	0.47	−0.14	−0.31	0.04	
Per cent energy protein	12.91	2.86	13.48	2.63	−0.57	−1.16	0.16	2.46
Per cent energy fat	43.84	7.54	41.57	6.58	2.27	1.75*	0.22	4.67*
Per cent energy carbohydrate	39.59	6.18	41.76	6.52	−2.17	−1.77*	0.18	3.09
Alcohol	0.24 g	0.40	0.24 g	0.40	0.00	0.04	0.04	
Sucrose	1.57 g	0.97	1.57 g	1.17	0.00	0.003	0.12	
Cellulose	97.56 mg	36.72	109.37 mg	33.88	−11.81	−1.68*	0.18	3.09
Lignin	18.62 mg	16.72	22.07 mg	18.03	−3.45	−1.00	0.14	1.87
Non-cellulose	263.86 mg	113.50	303.90 mg	115.09	−40.04	−1.74*	0.20	3.84
Total fibre	380.21 mg	157.71	435.29 mg	147.74	−55.08	−1.80*	0.24	5.52*
Vitamin A	108.64 i.u	65.67	98.66 i.u.	42.01	9.98	1.17	0.12	
Thiamine	22.51 μg	7.21	23.33 μg	7.96	−0.82	0.31	0.02	
Niacin	0.32 mg	0.12	0.32 mg	0.14	0.00	0.01	0.08	
Riboflavin	0.03 mg	0.01	0.03 mg	0.01	0.00	0.24	0.06	
Vitamin B6	31.19 μg	11.26	32.93 μg	11.98	−1.74	−0.68	0.06	
Folic acid	1.58 μg	1.07	1.35 μg	0.59	0.23	1.87*	0.08	0.62
Vitamin C	1.17 mg	0.76	1.19 mg	0.74	−0.02	−0.11	0.12	
Calcium	17.98 mg	7.59	19.83 mg	8.92	−1.85	−1.13	0.14	1.87
Iron	0.33 mg	0.31	0.30 mg	0.20	0.03	0.89	0.06	
Phosphorous	27.54 mg	9.29	28.90 mg	9.67	−1.36	−0.78	0.10	
Magnesium	5.55 mg	2.26	5.78 mg	2.00	−0.23	−0.55	0.14	
Sulphur	16.17 mg	4.46	16.84 mg	5.29	−0.67	−0.77	0.10	
Sodium	46.32 mg	15.52	49.61 mg	21.60	−3.29	−0.86	0.18	
Potassium	63.23 mg	22.36	66.83 mg	21.58	−3.60	−0.79	0.12	
Water	42.10 mg	14.92	45.68 mg	17.91	−3.58	−1.03	0.14	1.87
Oxalate	3.03 mg	1.33	2.93 mg	1.57	0.10	0.33	0.08	
Purine nitrogen	1.99 mg	0.81	2.24 mg	1.06	−0.25	−1.52	0.14	1.87

* $0.10 < P > 0.05$

the Kolmogorov-Smirnov statistic and the chi-square values were relevant.

It may be noted from the Table that the 0.05 level of significance was not attained by any of the nutrients but an 0.10 level of significance was attained by cellulose, non-cellulose, total fibre, folic acid, percentage of energy from fat and percentage of energy from carbohydrate with the paired t-test; the chi-square values gave a similar level of significance in the case of total fibre intakes and the percentage energy from fat. A negative t-ratio indicates that the kidney stone group had lower intakes of that nutrient than the control group.

It should be understood that there is some degree of interdependence between the nutrients and that no attempt to quantify it has been undertaken here. What is apparent, however, is that each of the statistical tests indicates that, relative to other nutrients investigated, fibre intake and percentage energy from carbohydrate were noticeably higher in the non-kidney stone group, and that percentage energy from fat was noticeably higher in the kidney stone group.

Discussion

Renal stone patients were grouped together for the purpose of the dietary analysis regardless of the presence of any underlying aetiological factors such as hypercalciuria or cystinuria. This grouping may underestimate the effect of dietary factors in the so-called "idiopathic" renal stones, but sub-grouping of the dietary results according to the presence or absence of serum or urinary abnormalities would have presented "small number" problems in statistical analysis.

The methodology used for collecting the initial dietary information was such that great precision of intake levels could not be expected, since it involved a 7-day dietary recall technique with average daily intakes calculated as one-seventh of weekly intake. This source of error may have unfavourably influenced the confidence levels.

The results (Table) show differences between 3 dietary factors:

1. Dietary fibre intake was consistently higher in the control group. Studies carried out on the effect of dietary fibre in man (Gibbon, 1975, 1978 (personal communication); Kelsay, 1978) suggest that it affects the absorption of minerals, blood calcium levels, fat absorption, bile acid secretions, urinary calcium and oxalate excretion.
2. The percentage of energy from carbohydrate was also consistently higher in the control group. This may be related to the dietary fibre intake because fibre-rich cereals, vegetables and fruit also contain a considerable proportion of carbohydrate.
3. The percentage of energy from fat was consistently higher in the kidney stone group and dietary fat, like vitamin D, can affect the absorption of calcium and phosphate from the diet. This illustrates the inverse association between energy provided by fat and carbohydrate. When the percentage of energy from fat is high in a diet, the percentage of energy from carbohydrate or protein is correspondingly lower.

In addition to the intake of individual nutrients, the combination of nutrient intakes in the diet is also an important determinant of biological effects, arising from metabolic interdependence. This should be kept in mind in studies where nutrient intakes are assessed and compared individually.

In a study such as this, one can only hope to determine preliminary indications of differences in the nutrient intake of stone patients, but further research on the effect of high fibre, low fat diets on the recurrence of kidney stones may help to verify these findings.

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Ureteric Obstruction of Solitary Kidneys by Aneurysms of the Iliac Artery

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Summary—Two rare cases are reported, both known to have solitary kidneys, that had ureteric obstruction caused by iliac artery aneurysms. Iliac aneurysms have a high mortality and may present to the urologist as an uncommon cause of ureteric obstruction. When the ureter of a solitary kidney is obstructed it is recommended that both ureterolysis and a temporary proximal diversion be performed. A common iliac aneurysm should be excised and grafted where possible; an internal iliac aneurysm is best treated by simple ligation or partial excision only.

Although iliac aneurysms may be extensions of abdominal aortic aneurysms, they do occur either separately or in isolation. The incidence of an iliac aneurysm is thought to be about one-tenth that of an abdominal aortic aneurysm (Markowitz and Norman, 1961; Silver *et al.*, 1967). Aortic aneurysms are now well known to cause ureteric obstruction (Peters and Cowie, 1978) but the ability of an iliac aneurysm to cause ureteric obstruction is less well known and may be overlooked.

The following 2 case reports demonstrate some of the difficulties in diagnosis and management.

Patients

Patient 1. A 61-year-old man was admitted to hospital with a 6-day history of lower abdominal pain and anuria for 24 h. From his past history he was known to have an absent right kidney.

On examination he was drowsy. The blood pressure was 210/130 mmHg and he was oedematous. On abdominal palpation he was tender in the left iliac fossa and no bowel sounds were heard. He was catheterised and the bladder was found to be empty. The electrolytes were abnormal, the blood urea was 35.7 mmol/l, the creatinine 850 μmol/l, and the potassium was 6.4 mmol/l. A high dose intravenous urogram confirmed the absence of the right kidney and showed a large obstructed left kidney and no ureter was demonstrated.

Cystoscopy was performed under local anaesthesia and a catheter passed up the left ureter which immediately drained clear urine. The catheter was left in place and the patient improved over the next 48 h. He was then cystoscoped again and on this examination the left side of the bladder was seen to be pulsating. On rectal examination the left side of the rectum was

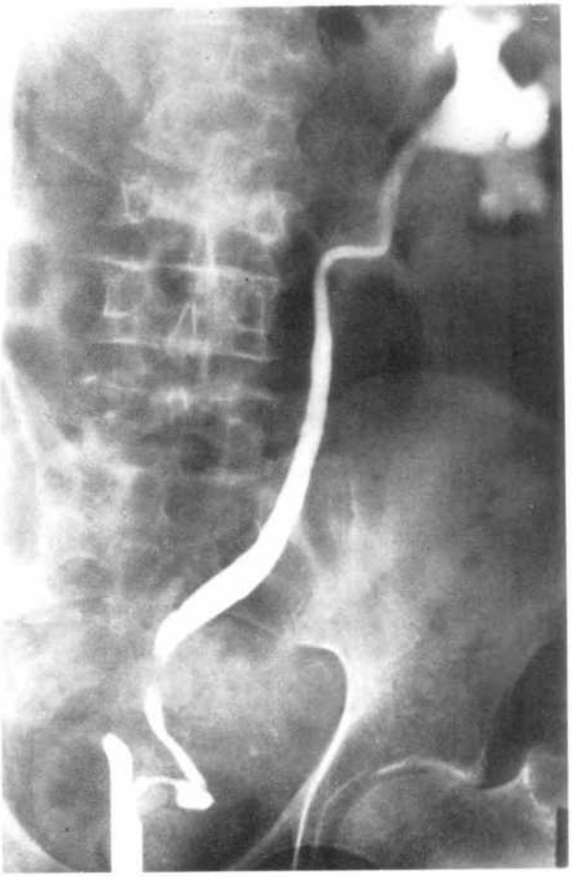

Fig. 1 Retrograde ureterogram demonstrating displacement of the lower third of the ureter and a constant filling defect with some proximal dilatation.

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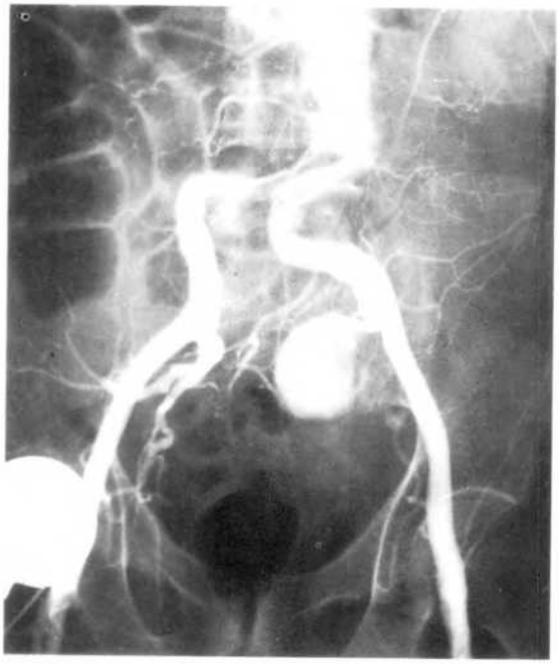

Fig. 2 Transfemoral arteriogram demonstrating an aneurysm of the left internal iliac artery.

pulsating. A retrograde ureterogram showed that the lower third of the ureter was displaced medially with a constant filling defect (Fig. 1). A pyelostomy was performed.

The patient continued to improve and his electrolytes began to return to normal. However, on the fifth day after his admission he developed a deep vein thrombosis in the left leg. A venogram showed extensive thrombosis in the right popliteal and femoral veins. The left external iliac vein was shown to be compressed and displaced laterally. He was anticoagulated uneventfully and improved.

On the twelfth day after admission a transfemoral arteriogram was performed which showed a large aneurysm of the left internal iliac artery (Fig. 2).

At laparotomy the ureter was found to be stretched over the aneurysm and involved in perianeurysmal fibrosis and blood clot. The ureter was dissected free. The internal iliac artery had a well defined neck which was ligated and no attempt was made to excise the aneurysm.

The patient initially made a satisfactory recovery but died 7 days later from myocardial infarction. The histology of the aneurysm was that of atherosclerosis.

Patient 2. A 60-year-old man was admitted with a history of lethargy, nausea and vomiting with a headache for some 5 days. He also complained of lower abdominal pain, polyuria and polydipsia. He had had a radical nephrectomy 2 years previously for renal cell carcinoma of the left kidney.

On examination the only abnormal finding was his blood pressure which was raised at 195/135 mmHg. His electrolytes were abnormal. The urea was 22.6 mmol/l and creatinine 484 μmol/l. The intravenous urogram showed dilated calices and pelvis with a dilated and displaced upper two-thirds of the ureter.

The retrograde ureterogram demonstrated a kink in the lower one-third of the ureter. This was attributed to possible involvement of the ureter in metastatic tumour and a laparotomy was performed.

At laparotomy a small common iliac aneurysm was found to which the right ureter was densely adherent. The ureter was freed and placed intraperitoneally. The aneurysm was considered unsuitable for resection and a marlex mesh was applied.

The patient made an excellent recovery. When seen 12 months later he was well, his blood pressure was stable and his intravenous urogram normal.

Discussion

It is perhaps surprising, in view of the anatomical relations of the iliac vessels to the ureter and the increasing incidence of atheroma, that there are so few cases recorded of ureteric obstruction by iliac aneurysms. Only 23 such cases have previously been reported (Redman and Campbell, 1975; Rennick *et al.*, 1976; Peterson *et al.*, 1977; Kaynan *et al.*, 1978), 10 involving the internal and 13 the external iliac artery. Only 2 of these cases had solitary kidneys (Peterson *et al.*, 1977). Thirteen were not diagnosed until laparotomy or post mortem and 3 required a second operation. The mortality of ruptured iliac aneurysms is high, ranging from 30 to 80% (Wirthlin and Warshaw, 1973); of those cases reported causing ureteric obstruction the mortality was 39%.

Iliac aneurysms produce their symptoms by pressure on adjacent organs in the pelvis, or by rupture, and may present to the general and orthopaedic surgeons as well as to the urologist. The patients present with varied urological symptoms (Silver *et al.*, 1967; Safran *et al.*, 1975). Flank pain resembles colic and may be related to ureteric obstruction or leakage of the aneurysm. Haematuria is usually due to erosion and fistula formation from mycotic or traumatic aneurysms (Taylor and Reinhart, 1939; Rennick *et al.*, 1976). Urinary tract infections have been reported related to obstruction. A number of patients have presented with prostatic symptoms due to the distortion of the bladder neck as well as the alarming symptom of a pulsatile urinary stream (Frank *et al.*, 1961; Silver *et al.*, 1967). Oliguria has also been described with bilateral ureteric obstruction due to an enormous aneurysm (Goodwin and Schumacker, 1947; Smith *et al.*, 1977). Examination may not be helpful since only 20% of iliac aneurysms are palpable compared with 88% of aortic aneurysms (Wise and Mason, 1975). There may, however, be a degree of tenderness, particularly if the aneurysm is leaking, and there may be a bruit over the abdomen. Rectal examination often reveals a pulsatile mass and the prostate may be displaced. However, the diagnosis will often be made or suspected on intravenous urogram and cystoscopy with retrograde ureterogram. An iliac artery aneurysm should not be overlooked in cases of low ureteric obstruction and arteriography should be considered early in the patient's investigation.

In the surgical management the ureter should be freed and, in the case of a solitary kidney, a temporary nephrostomy or pyelostomy is advisable (Peterson *et al.*, 1977). A common iliac aneurysm will usually require grafting with total or partial excision of the aneurysm with a trouser graft if there is bilateral or aortic disease. The average diameter of ruptured common iliac aneurysms has been reported as 5.4 cm, the minimum diameter as 4 cm. After freeing the ureter it may therefore be possible surgically to correct the aneurysm later if it is less than 4 cm and not leaking (Thiele *et al.*, 1975). An internal iliac aneurysm, if it has a neck, may be simply ligated. If it is very large, total excision should be avoided as it is difficult to obtain distal control; in this situation partial excision and obliteration of the remnant are advisable (Kirkland and Starr, 1953; Short, 1966; Wirthlin and Warshaw, 1973). If an internal iliac aneurysm is found incidentally it is recommended that it is ligated only.

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Ileal Conduit Urinary Diversion in Children. An Assessment of the Long-term Results

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Summary—Forty-three children who underwent cutaneous ureteroileostomy are described. Particular attention has been paid to long-term follow-up, which has produced disappointing results. Deterioration occurred in 61% of the kidneys studied and although recurring urinary tract infections and stomal problems occurred in many patients, no single factor could be implicated as the cause of deteriorating renal function.

Forty-three children who underwent cutaneous ureteroileostomy were studied in order to assess their upper urinary tract function after diversion.

Patients

From 1958 to 1971, 43 infants and children underwent urinary diversion in the form of a cutaneous ureteroileostomy using the technique, with modifications, described by Bricker (1950). There were 20 males and 23 females. The age at operation ranged from one to 13 years. The primary diagnosis is shown in Table 1 and the indications for operation in Table 2. Incontinence of urine, which was present in all patients, was the primary indication for surgery in 23. In 3 out of 4 patients with ectopia vesicae direct surgical procedures had failed. The patient with an ectopic ureter had been operated on but incontinence continued.

Operation

The technique has been fully described by Kirkland (1978). In summary, a suitable length of ileum was isolated and its proximal end closed. The ureters were anastomosed separately by simply "fish-tailing" the mobilised ureters and drawing them with silk sutures through a submucous tunnel. They were fixed with silk sutures passed through all layers of the ileum. The anastomoses were covered with peritoneum so that they remained extraperitoneally.

Table 1

Primary diagnosis	*Number*
Myelomeningocele	34
Ectopia vesicae	4
Spinal tumour	2
Obstructive uropathy	1
Ectopic ureter	1
Anorectal atresia with sacral agenesis	1
Total	43

Follow-up

Following surgery, patients were reviewed on a 6-monthly basis. Early in the series intravenous urography was carried out on a 2-yearly basis. Later, investigation with renogram and renal scan was introduced. A catheter specimen of loop urine was taken for culture at each visit and, if indicated clinically, blood urea and electrolytes were assessed. The length of follow-up in this series was from 4 to 22 years with an average of 15 years after surgery.

Results

Early Complications

These were defined as occurring within one month

Table 2

Primary indication for operation	*Number*
Incontinence of urine	23
Deterioration of upper urinary tract	16
Failure of other surgery	4

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of urinary diversion and are shown in Table 3. One patient developed urinary peritonitis and wound dehiscence post-operatively.

Late Complications

Eleven of our 43 patients have had no complications on follow-up. The remaining 32 have had a variety of problems, some requiring further surgery, and these are summarised in Table 4. The majority relate to the ileal stoma with evidence of retraction, prolapse or stenosis. To date there have been 27 stomal revisions in 14 patients. Six revisions have been necessary for stenosis, while another 4 have been for reduction of the loop following lengthening with growth. Six patients developed calculi and in 4 of these the calculi were situated in the ileal loop. One patient had recurrent calculi associated with chronic infection in a single kidney. She required multiple operations, including conversion of her ileostomy to a cutaneous ureterostomy. Ureteroileal stenosis occurred in 3 patients, who underwent successful reimplantation of the ureter. A further 3 patients required cystectomy for pyocystitis, one showing early mucosal metaplasia in a bladder that had been isolated for 3 years. One child with recurrent infection showed gross reflux into both ureters, but prior to operation had been noted to have hydroureters. Another patient developed a partial infarction of the ileal stoma 6 months post-operatively; this was due to an ill-fitting appliance strangulating the ileal spout. Three patients required dialysis for chronic renal failure; one of them ultimately underwent renal transplantation.

Radiological Status of the Upper Urinary Tract

Pre-operative intravenous urograms were available in 42 of the 43 patients studied. One patient died on the third post-operative day. Two further patients had only single kidneys. Thus only 42 patients with a total of 80 renal units could be assessed radiologically both before and after operation. The results of this comparison are shown in Table 5.

Table 3

Early complications	*Number*
43 patients	
None	36
Wound dehiscence	2
Urinary peritonitis	2
Infarcted ileal loop	1
Adhesive obstruction	1
Ureteroileal stenosis	1
Death	1

Table 4

Late complications	*Number*
43 patients	
None	11
32 patients	
Stomal revision	27 in 14 patients
Calculi	6
Redundant ileal loop	4
Ureteroileal stenosis	3
Pyocystitis	3
Chronic renal failure	3
Conversion to ureterostomy	2
Infarction of ileal stoma	1
Gross ureteric reflux	1
Deaths Renal 2 Non-renal 2	4
Dialysis	2
Renal transplant	1

Discussion

Reports have recently appeared in the literature reviewing the results of ileal conduit urinary diversion in children. Some have demonstrated deterioration of the upper urinary tract in only a few patients (Delgado and Muecke, 1973; Stevens and Eckstein, 1977). However, reservation as to the place of this procedure in the management of neuropathic bladder in childhood was first voiced by Smith (1972) and later supported by reports from Scott (1973) and Middleton and Hendren (1976). The conflicting opinions were discussed by Cass (1976b) and a number of series were reviewed by Ritchie (1974). The contradictory views expressed may be less anomalous when the average length of follow-up in each series is considered (Shapiro *et al.*, 1975). Amongst the few who have

Table 5 Radiological Assessment of the Upper Urinary Tract

Before diversion		*After diversion*		
	Number of renal units	*Number of renal units*		
		Improved	*No change*	*Deteriorated*
Normal	48		21 (44%)	27 (56%)
Abnormal	32	3 (9%)	7 (22%)	22 (69%)
Total	80	3 (4%)	28 (35%)	49 (61%)

analysed their cases for periods greater than 10 years are Schwarz and Jeffs (1975), Shapiro *et al.* (1975), Smith (1978) and Pitts and Muecke (1979). Middleton and Hendren (1976) stated, "We suspect that other surgeons will note an increase in the incidence of renal deterioration with longer observations of their cases." We have followed our patients for up to 22 years (average 15 years) and noted an overall deterioration rate of 61% (Table 5), results which support this claim.

As has been found in other series (Smith, 1972, 1978; Pitts and Muecke, 1979), deterioration occurred less frequently in those units diverted before damage had occurred, but a rate of 56% in our series is still disappointing. Although no single factor could be shown as the cause of this deterioration, a number of factors may contribute.

Ileal stomal stenosis is recognised more often than in the past. Hardy *et al.* (1977) would appear to recognise this cause with resultant back pressure affecting the upper urinary tract. Although stomal revision was required on 27 occasions, in only 6 was this performed for stenosis. There was no correlation between the latter patients and deterioration of the upper urinary tract.

Infection occurred in 31 (75%) of our cases post-operatively. Ritchie *et al.* (1974) have shown in animal experiments that refluxing infected urine from the conduit will cause deterioration of the upper urinary tract. Infection has also been shown to disturb normal peristalsis in the ureter with subsequent loss of propulsive power (Ross *et al.*, 1972). However, no significant correlation between the presence of infection and deterioration of the upper urinary tract was found in our series.

No attempt was made to grade the degree of deterioration. This ranged from mild dilatation of the collecting systems to severe hydronephrosis. Although the intravenous urogram provides a satisfactory anatomical assessment of the upper urinary tract, the absence of gross biochemical change does not exclude deterioration in tubular function, which in most cases precedes deterioration of glomerular function (Walker *et al.*, 1977). Whereas 49 out of 80 kidneys had deteriorated on intravenous urography (61%) (Table 5), only 3 patients have so far shown biochemical evidence of renal failure. Two have required dialysis, one of these proceeding to renal transplantation. The increasing use of radioisotope techniques may allow earlier determination of decreasing renal function to be made (Orr *et al.*, 1979).

It could be argued that our poor results arose from faulty initial surgical technique; however, this should be reflected in a high early complication rate and this was not so. The rate of 16% is comparable with that of other series: 31% (Delgado and Muecke, 1973); 18% (Middleton and Hendren, 1976) and 28% (Stevens and Eckstein, 1977).

If not a feature of operative technique, the disappointing results are a reflection of the longer period of follow-up.

Little comfort can be taken from the fact that these results are an improvement on what would be expected if diversion had not been undertaken, where at 10 years, 90% of females and 60% of males will show renal deterioration (Mebust *et al.*, 1969).

What should be the approach to those patients requiring diversion in the future? Unfortunately at present there is no clear answer. Although the number of children requiring diversion has diminished in the United Kingdom because of the decreasing number presenting with neuropathic bladder, treatment is still required in a small but important group. In this unit no ileal conduit diversions have been carried out in the past 7 years, the result of a more conservative approach to treatment. Greater use has been made of procedures which overcome obstruction distal to the bladder. Intermittent catheterisation techniques (Lyon *et al.*, 1975) and the use of indwelling silastic catheters (Duthie and Stark, 1974) have given early but probably temporarily encouraging results. A conservative approach is, however, not universally acceptable. Cass (1976a) reported disappointing results with these regimes. In the male, social control of incontinence may be achieved by fitting a non-return valve urinal, but the female still requires some form of operative treatment.

Bilateral cutaneous end ureterostomies protect renal function, but unless the ureters are long enough to be brought together in the midline to allow for one stoma, bilateral ureterostomies can create difficulties resulting from poor collecting bag application. It is, however, a satisfactory temporary diversion.

Ureterosigmoidostomy as an alternative diversion is favoured by some (Aaronson and Morgan, 1978), but is not applicable in the majority of incontinent patients with a neuropathic bladder. More experience has been gained with the use of non-refluxing sigmoid conduits (Mogg, 1970; Hendren, 1976). In laboratory studies there has been a significantly lower incidence of pyelonephritis in kidneys diverted through a non-refluxing sigmoid conduit compared with those where the mode of diversion has been an ileal loop (Hendren *et al.*, 1978). The short-term results of clinical experience with this technique reveal a complication rate significantly less than that seen previously in patients with ileal loop diversion (Althausen *et al.*, 1978). Due to the lack of long-term experience with this technique, ileal loop diversion remains the standard against which other methods must be measured. Our experience has illustrated that, with longer periods of follow-up, deterioration will continue to occur in the upper urinary tracts of those children thus diverted.

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Ureterocele in Bilharziasis of the Urinary Tract

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Summary—Five cases of ureterocele secondary to bilharziasis of the urinary tract are presented and discussed. It is important to be aware of this complication in an area where bilharziasis is endemic.

A ureterocele is a congenital cystic dilatation of the submucosal segment of the intravesical ureter (Tanagho, 1972). The diagnosis is usually made on an excretory urogram, when the typical "cobra head" deformity is present. The cystoscopic appearance is that of a semitranslucent cyst undergoing periodic inflation and deflation. Radiological appearances akin to those of a ureterocele have also been reported in association with vesical neoplasm (Sherwood and Stevenson, 1969; Cabanas *et al.*, 1973; Morse *et al.*, 1974) and ureteric calculus (Datta *et al.*, 1972). In the above conditions, however, a true cystic dilatation of the ureter was absent. We wish to report that bilharziasis of the urinary tract may occasionally lead to a cystic dilatation of the intravesical segment of the ureter, with a typical cobra head configuration on urography (Fig. 1). Our observations on 5 patients (7 ureteroceles) with severe urinary tract bilharziasis form the basis of this report (Table).

Pathogenesis and Cystoscopic Appearance

Histological examination of the dilated segments was performed in 3 cases and all showed severe fibrosis of the muscle walls together with deposition of ova to a marked degree. At cystoscopy the orifices of the affected ureters appeared stenosed. Thus it seems that the basic lesions in the pathogenesis of a ureterocele in urinary bilharziasis are a combination of meatal stenosis and attenuation of the muscular lining of the intravesical ureter. Stenosis of the ureteric orifice (not an uncommon lesion in vesical bilharziasis) when acting singly is unlikely to lead to such a localised dilatation of the ureter.

At cystoscopy the bilharzial ureterocele appears as an oblong and opaque cyst situated lateral to a normally placed ureteric orifice (Fig. 2). Its periodic contraction is appreciably sluggish, due probably to atonia of the segment. By contrast, the usual ureterocele appears as a semitranslucent cyst with the ureteric orifice located on its surface, and commonly demonstrates a pronounced cyclic filling and emptying.

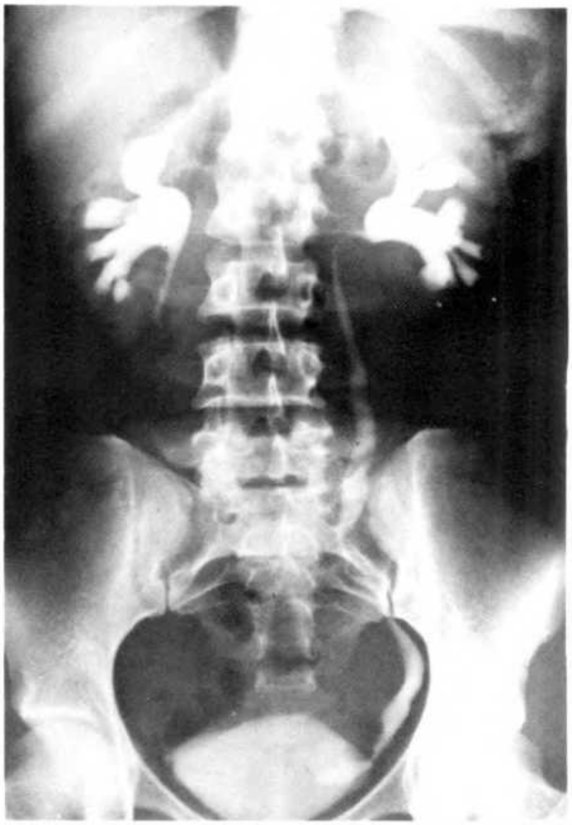

Fig. 1 Left-sided ureterocele producing the typical "cobra head" configuration in the urogram: associated ureteric dilatation and hydronephrosis.

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Table

No.	Age	Sex	Presentation	Urogram findings
1	40	M	Bilateral loin pain	Bilateral ureteroceles Dilated lower ureters
2	38	M	Left loin pain	Left ureterocele containing a small calculus Left hydroureter and hydronephrosis
3	25	F	Right loin pain	Bilateral ureteroceles Right hydronephrosis and hydroureter Fullness left calices
4	12	F	Terminal haematuria	Right ureterocele Normal upper and lower tracts
5	29	M	Left loin pain	Left ureterocele containing a small calculus Left hydroureter and caliceal fullness

Discussion

The formation of a ureterocele in bilharziasis of the urinary tract has received little mention in the English literature. Its clinical significance lies in the fact that the majority of bilharzial ureteroceles are symptomatic and are prone to develop complications if left untreated. It is probable that in the absence of any clinical suspicion and of a preliminary urogram, such a lesion, because of its sluggish cyclic activity, is likely to be overlooked during routine cystoscopy. Its incidence is thus difficult to establish. However, Umerah (1977), while reviewing urograms of 115 patients with bilharziasis of the urinary tract, observed cobra head deformity in the lower ends of 2 ureters. Thus an awareness of this complication and its characteristic cystoscopic appearance is important in an area where bilharziasis is endemic.

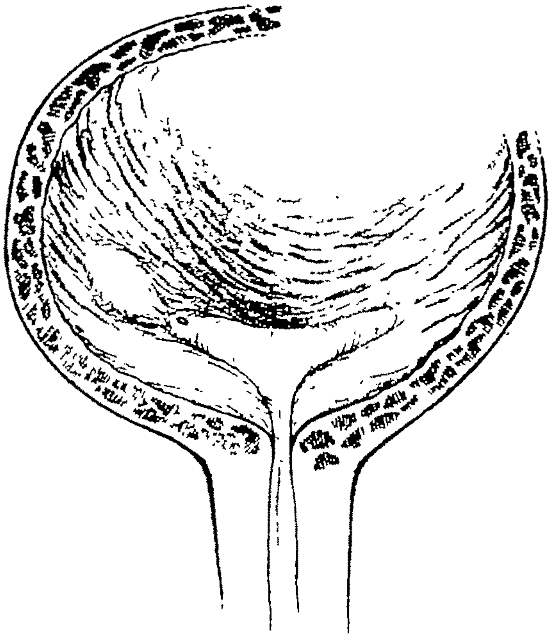

Fig. 2 Cystoscopic appearance of a bilharzial ureterocele on the right.

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The Use and Mechanism of Anal Sphincter Stretch in the Reflex Bladder

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Summary—Anal sphincter stretch enables good bladder emptying with excellent continence in some paraplegics with reflex bladders. It produces relaxation of both the external urethral sphincter and the detrusor, and micturition is achieved by abdominal straining.

Anal sphincter stretch is a voiding technique useful in some patients with reflex bladder lesions. It involves digital stretching of the anal sphincter followed by abdominal straining to produce voiding. Its use was originally prompted by the observation that some patients with upper motor neurone lesions of the bladder were able to pass significant volumes of urine during manual emptying of their rectum. Although there are earlier reports on the effect of anal stretch and anal stimulation on bladder function (Kock and Pompeius, 1963; Rossier and Bors, 1964; Sundin *et al.*, 1974), the first paper on its clinical application was by Kiviat *et al.* (1975) where they reported its use in 16 patients. This was followed by a second paper (Donovan *et al.*, 1977) in which 26 patients who successfully used this method were reviewed. In this latter paper, urodynamic and EMG studies in 3 patients suggested the mechanism of anal stretch and we have been able to confirm these findings in a number of paraplegics.

Technique

Anal stretch is carried out by the patient, sitting on a commode, inserting one or 2 gloved fingers just through the external anal sphincter and stretching this muscle until it is felt to relax. Once this occurs, abdominal straining of the Valsalva type is used to produce voiding, and is continued until the bladder is thought to be empty. Often the stretch has to be applied several times followed by straining until no more urine can be produced. Because the method requires relatively normal power in the intrinsic muscles of the hand, as well as the ability adequately to raise the intra-abdominal pressure, it is most effective in patients whose spinal cord lesion is below the mid-thoracic level. The procedure also tends to be more useful when the paraplegia is relatively complete, since the force necessary to bring about relaxation of the sphincter often causes pain when significant perineal sensation is retained. Donovan *et al.* (1977) have reported the use of a non-elastic abdominal corset and a plastic digit to extend the use of anal stretch to high thoracic lesions and even some quadriplegics, but these additional appliances have not been successfully employed by us to date.

Results

Six patients who regularly use anal sphincter stretch have been followed by the authors at the Royal Perth (Rehabilitation) Hospital. Two of them discovered the technique for themselves during manual removal of faeces. The neurological status and degree of continence of the 6 patients are shown in Table 1. As can be seen, all are mid or low thoracic spinal cord lesions apart from one patient with a T5 lesion, and 3 are females. Five of them are almost completely continent apart

Table 1

Patient	*Sex*	*Age*	*Lesion*	*Continence*
W.M.	M	31	Complete below T5	Fair
D.D.	M	29	Complete below T8	Excellent
R.McG.	M	26	Complete below T12	Excellent
D.S.	F	46	Complete below L1	Excellent
H.G.	F	38	Incomplete below L1	Excellent
L.O'B.	F	26	Incomplete below L2	Excellent

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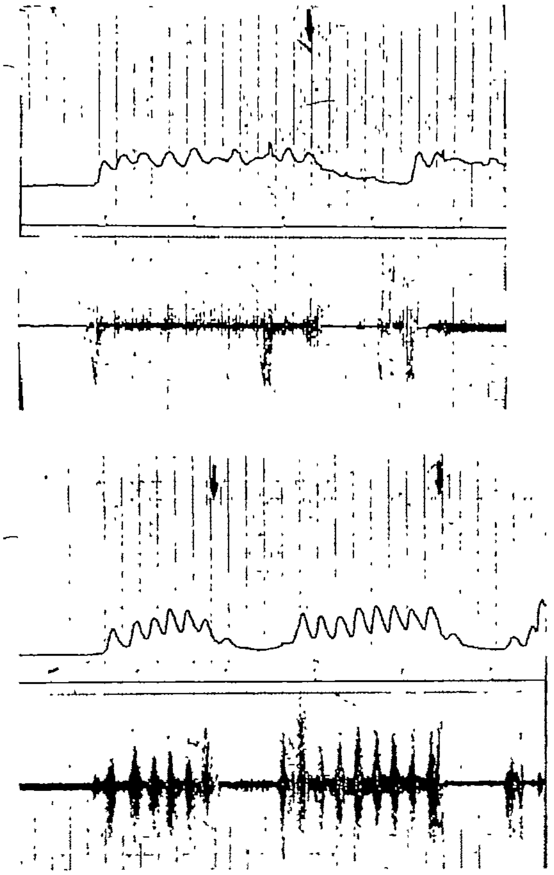

Figs. 1 and 2 Cystometric studies in 2 patients showing the effect of anal sphincter stretch. The upper tracing shows intravesical pressure and the lower the EMG of the external urethral sphincter. Arrows indicate the point at which anal stretch has been applied with resultant cessation of the detrusor contraction as well as of EMG activity. Release of anal stretch is followed by return of both functions.

from when they develop a urinary infection and, except for the patient with the T5 lesion, require no urinary collecting devide. The procedure has proved unsuccessful in other patients of similar neurological status, for a variety of reasons (Table 2). In 5 of these 12 patients no effect could be shown at cystometry either on the detrusor contraction or on the EMG tracing of the external sphincter. Two patients had partial abolition of both detrusor and sphincteric activity, but voiding was only of small volume in one and absent in the other. One male with a low thoracic lesion had an excellent cystometric response to anal stretch but was never able to micturate by straining in spite of good abdominal musculature. A satisfactory response followed by adequate bladder emptying was achieved in 3 patients but the method had to be abandoned in 2 females because of gross faecal incontinence on each occasion, and the third patient, a male, found the procedure repugnant and refused to continue using it.

This aversion to inserting a finger into the rectum was found in a number of other patients (not included in Table 2), thus rendering assessment of its effect impossible. One female patient with an incomplete lower motor neurone lesion attempted the method but found it produced only faecal incontinence without any voiding.

Taking both groups together, of 18 patients studied 9 (50%) had evidence of obliteration of detrusor and sphincteric contractions with satisfactory voiding, but only 6 ($33\frac{1}{3}$%) were able to use anal stretch successfully as their principal means of bladder emptying.

Discussion

Kiviat *et al.* (1975) and Donovan *et al.* (1977), using EMG studies of the external anal and urethral sphincters, demonstrated that anal sphincter stretch after, in some instances, an initial increase in electrical activity, produced definite relaxation in both sphincters. It was originally thought that this relaxation was accompanied by stimulation of a detrusor contraction and indeed the technique was initially mistakenly known as "anal stimulation". Later studies by Donovan *et al.* (1977), and subsequently by ourselves, have shown that far from stimulating the detrusor, anal stretch actually abolishes its activity, thereby producing a simultaneous relaxation of the external urethral sphincter and the detrusor. Micturition is then achieved by raising the intra-abdominal pressure using the Valsalva manoeuvre while the outflow resistance is thus lowered. Phenoxybenzamine has been used to lower urethral pressure further (Krane and Olsson, 1973) in 4 patients during their early use of anal stretch, but only one of them is currently taking this drug.

Most paraplegics with upper motor neurone lesions of their bladders have detrusor-sphincteric dyssynergia and, in many of them, this produces sufficient outflow obstruction to cause difficulty in adequate bladder emptying, and may also progressively increase intravesical pressure during detrusor contraction, with the associated risks of infection and vesicoureteric reflux. The usual treatment for this problem is endoscopic division

Table 2

Patient	*Sex*	*Age*	*Lesion*	*Result*		
				Abolition of detrusor and sphincter activity	*Voiding*	*Other*
M.P.	M	21	Incomplete below C5	Nil	Nil	
P.D.	M	20	Complete below C7	Nil	Nil	
W.S.	F	46	Incomplete below C7	Slight	Slight	
P.H.	F	38	Complete below C8	Nil	Nil	
P.C.	F	17	Complete below T4	Good	Good	Faecal incontinence
T.T.	M	27	Complete below T4	Nil	Nil	
A.L.	M	35	Incomplete below T4	Slight	Nil	
M.G.	F	22	Complete below T8	Nil	Nil	
T.A.	M	20	Complete below T10	Good	Good	Unwilling
E.B.	F	72	Incomplete below T12	Good	Good	Faecal incontinence
A.F.	M	23	Complete below T12	Good	Nil	
G.P.	F	66	Incomplete LMN lesion	?	Nil	Faecal incontinence

of the external sphincter, but this brings about a greater degree of incontinence in many patients and is not applicable to the female. Anal stretch, by relaxing the external urethral sphincter, overcomes this increased outflow resistance and allows the bladder to be emptied at a relatively low pressure by straining. Provided that the functional bladder capacity is reasonably large, *i.e.* that reflex detrusor contractions are not precipitated by too low an intravesical volume, the patient is able, with sensible regulation of fluid intake, to employ anal stretch at intervals, *e.g.* 3 to 4 times per day, and remain dry in between. In those patients in whom it is effective, therefore, the manoeuvre not only overcomes the serious problem of detrusor-sphincteric dyssynergia, but also allows excellent and often complete continence, a situation of particular importance in the female in whom no satisfactory external urinary collection device is yet available. It is also interesting that one of our patients (R.McG.) was able to void well, using anal stretch, for many weeks before any cystometric evidence of detrusor activity could be demonstrated. We therefore believe that the technique is worth trying as part of bladder training from a relatively early stage, *i.e.* 6 to 8 weeks after the accident, even if still wearing a body jacket, in those paraplegics able to raise their intra-abdominal pressure significantly.

It is concluded that anal sphincter stretch has been shown to produce relaxation of the external urethral sphincter accompanied by inhibition of detrusor contraction and to rely on increased intra-abdominal pressure to bring about voiding. We believe it to be a very useful technique in some paraplegics, especially those who retain reasonable abdominal musculature, for when effective, it enables very adequate bladder emptying along with excellent urinary control.

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An Appraisal of 12 Solutions Used for Bladder Irrigation or Instillation

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Summary—Twelve solutions used for bladder irrigation or instillation have been reviewed. The advantages and disadvantages of the solutions are discussed and a regimen is suggested for intermittent 6-hourly catheterisation procedures using the mixtures polymyxin/neomycin and EDTA/lysozyme alternately.

The use of solutions for bladder irrigation and prevention of infection due to catheterisation has been a continuing subject for study, as evidenced by the literature published over the past 30 years. No one solution has been entirely satisfactory, either because its range of antibacterial activity has been limited or because it has caused tissue damage. This paper reviews the literature on 12 solutions. It is hoped that the drawing together of this information into one article will help urologists to select solutions for use in bladder irrigation or instillation.

The following solutions have been reviewed: acetic acid, amphotericin B, chlorhexidine digluconate, EDTA/lysozyme, framycetin (Soframycin) kanamycin sulphate, kanamycin-colistin, neomycin sulphate, nitrofurazone, noxythiolin (Noxyflex), polymyxin B—neomycin and povidone-iodine (Betadine).

Acetic Acid

The bacteristatic effect of low pH has been used as preventive treatment for catheter-induced urinary tract infections (Kunin, 1974). Kass and Sossens (1959) irrigated continuously at 1 ml/min with 0.25% acetic acid in physiological saline. The solution was retained in the bladder for 55 min by clamping the outlet tube, and then releasing it for 5 min. Using this procedure they found an infection rate of less than 1%. Martin (1967), however, using a bactericidal concentration of 1% acetic acid rinse, reported an infection rate of 17%. The major disadvantages with the acetic acid solution are: the time necessary for adjusting flow rates and clamping; the danger of confusion with ordinary intravenous fluids (this may be avoided with proper labelling and colouring the solution) and its being bacteristatic at a concentration of 0.25% (Kass and Sossens, 1959).

Also, irritation of the bladder has been noted even at 0.25% because of the low pH (<6.0) (Kunin, 1974), and surveillance of the pH is mandatory if irrigation is to be effective (Kass and Sossens, 1959).

Amphotericin B

The fungicide amphotericin B (100 mg/l) has been used successfully for treating a number of systemic mycotic infections (Takacs *et al.*, 1963). A regimen of 5 consecutive 2-hourly instillations of an aqueous solution of amphotericin B 50 mg in 500 ml of distilled water has been highly successful in eliminating *Candida* infections of the bladder in patients with spinal cord injury (Pearman and England, 1973). No untoward side effects have been observed clinically following the use of this treatment in over 50 patients during the past 7 years (Pearman, 1977). Bladder irrigation with 5 mg/l has also been used by Kunin (1974) in conjunction with intravenous administration. However, amphotericin B has been shown to be toxic in both humans and animals when given systemically. Weldon and Shultz (1974), in their animal studies with amphotericin B, showed that swelling (with some hyperplasia of the glomeruli and interstitium) was present and also that amorphous casts or irregular solid deposits containing calcium salts ruptured the tubules. The glomerular and interstitial changes were ascribed to ischaemia caused by renal tubular acidosis disrupting the tubule cells of the membranes. The

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drug combines with sterols in the cell membrane, resulting in increased permeability, leakage of cell contents and final destruction of the cell (McCurdy *et al.*, 1968). These observations raised the possibility that topical instillations or irrigation may also damage the epithelial cells of the bladder (Harper, 1979).

Chlorhexidine Digluconate

Chlorhexidine is related to proguanil and is one of the most active diguanides. It was first synthesised in 1954 by Davies *et al.* and has been extensively used in medical practice in the United Kingdom, Western Europe and Australia for over 20 years. Chlorhexidine is effective against a wide range of bacteria (Davies *et al.*, 1954; Calman and Murray, 1956; Lawrence, 1960; Hugo and Longworth, 1964, 1965). However, there have been occasional reports of bacterial resistance (Gillespie *et al.*, 1967; Stickler, 1974). It has been shown that some bacteria, especially *Pseudomonas*, have a high intrinsic resistance to chlorhexidine and have been found growing in solutions of chlorhexidine. As a precaution it has been suggested that aseptic conditions should be maintained as far as possible and that only sterile distilled water complying with the pharmacopoeial standards be used (British Pharmacopoeia, 1973). The use of demineralised H_2O is not advocated, since ion-exchange resins provide excellent growth conditions for many bacteria. Another precaution that needs to be observed in the use of chlorhexidine solutions is care in their storage. Linton and George (1966) have shown that the tannins in bark corks can inactivate chlorhexidine.

Because Beeuwkes and de Vries (1956) considered the effect of chlorhexidine on mucosal surfaces to be inconsequential, they advocated its use in urology. Paterson *et al.* (1960) reported that the instillation of 57 ml of a 1:5000 aqueous solution of chlorhexidine diacetate reduced the incidence of urinary tract infection caused by catheterisation from 70 to 13.5%, while Gillespie *et al.* (1964) showed that the incidence of infection was reduced from 93 to 14%. Mitchell and Gillespie (1962), MacFadyen and Simmons (1968) and Pearman (1971) reported similar results using 1:5000 chlorhexidine digluconate. However, Calman and Murray (1956) cautioned that concentrations in excess of 1:10,000 should not be used on delicate mucous membranes. Caldwell (1970) claimed that the use of toothpastes and mouth washes containing chlorhexidine resulted in a softening of the oral epithelium, thereby contributing to the formation of aphthous ulcers, and also retarded healing. Paterson *et al.* (1960) reported that the use of 1:5000 chlorhexidine diacetate caused haematuria in their patients. In addition to this there have been 2 further reports (MacFadyen and Simmons, 1968; Pearman, 1971) of a 1:5000 aqueous solution of chlorhexidine digluconate causing frank haematuria. Also, Harper and Matz (1975) demonstrated severe erosive reactions in rats after 24 to 48 hours' irrigation with chlorhexidine at 0.01%. However, they suggested that it may be used, since many procedures are brief and non-repetitive, unlike frequent intermittent catheterisation for several weeks following acute spinal cord trauma.

EDTA/Lysozyme

Goldschmidt *et al.* (1972) used urine diluted 1:4 and 1:16 to evaluate the *in vitro* effect of EDTA/lysozyme. They found that this solution significantly reduced the bacterial numbers of the micro-organisms tested. For clinical evaluation 2 types of experiment were performed: (*a*) the bladder was irrigated intermittently through a triple-lumen Bard-Foley catheter: 100 ml of solution was instilled for 30 min, drained and replaced with another 100 ml for a further 2 h; (*b*) alternatively, 150 ml of the solution was instilled into the bladder and the catheter clamped for 1 h. The patient was placed supine and then prone during the instillation. The solution was then drained and the procedure repeated after 4 h (Goldschmidt *et al.*, 1972). Of the 12 patients with *Pseudomonas* infections treated with EDTA/lysozyme bladder lavage, 8 were cleared of infection, 2 had significantly reduced colony counts, and 2 remained infected. A further 12 patients with bacteriuria underwent TUR and had their bladders irrigated with an EDTA/lysozyme solution. Four of these patients were free from bacteriuria at the end of this treatment.

However, Wooley and Blue (1974) found that Gram-positive bacteria were able to survive the EDTA/lysozyme solution *in vitro*, which suggested that this solution is not able to destroy the full range of urinary pathogens. This is possibly due to the higher content of techoic acid present in the cell wall of Gram-positive cocci (Cutinelli and Galdiero, 1967).

One patient during a cystostomy examination after EDTA/lysozyme lavage showed no sign of erosive cystitis (Goldschmidt *et al.*, 1972).

Framycetin (Soframycin)

The use of this solution has been reported by Bruce *et al.* (1971) on patients undergoing prostatectomy for benign prostatic hypertrophy and carcinoma. The report states that after an 8-h period of local hypothermia produced by catheter irrigation of the bladder with saline at 0°C, local irrigation with 333 mg/l of framycetin in water was performed over a 16-h period. Serum levels on the first 10 patients were all below 0.2 mg/l. They reported that absorption studies on dogs subjected to irrigation after prostatectomy showed no appreciable absorption of the antibiotic.

The report also states that patients with pre-operatively sterile urine who were irrigated with framycetin after surgery had an infection rate of 14% when the operation was performed electively, but that the rate was almost doubled (25%) when emergency surgery was performed. However, when patients with pre-operatively infected urine were irrigated with framycetin, the infection rate was 27% after elective surgery and 49% after emergency surgery. Bladder irrigation with framycetin provided better prophylaxis than parental administration of ampicillin in reducing the incidence of urinary tract infection after cystoscopy (Bruce *et al.*, 1971).

Kanamycin Sulphate

The 0.25% kanamycin sulphate solution which has been used as an operative irrigant on patients undergoing suprapubic prostatectomy or cystotomy has also been used to irrigate the bladder immediately before operation (Ciccone *et al.*, 1974). For periods up to, but not exceeding 1 h, 200 ml of kanamycin solution were left in the bladder.

There was low absorption from the bladder, serum concentrations of 1.4 and 1.0 mg/l being recorded at 1 and 6 hours respectively. This contrasts markedly with the absorption which can occur when kanamycin is used for intraperitoneal irrigation, when levels up to 8.4 mg/l in serum have been recorded. No allergic or local reactions to the kanamycin solution were noted.

Kanamycin-Colistin

Pearman (1977) reported that 130 patients (97 males and 33 females), admitted with acute spinal cord trauma during the period 1 February 1968 to 31 December 1973 and intermittently catheterised for more than 5 days, had a low incidence of urinary tract infection (UTI). The use of a kanamycin-colistin instillation solution after each catheterisation was a contributory factor to the low incidence of UTI, *i.e.* one episode of significant bacteriuria per 177 catheterisations (0.56%) in males and one episode per 103 catheterisations (0.9%) in females. However, it is significant that 93% of the micro-organisms isolated were resistant to both kanamycin and colistin. Furthermore, 60% of the organisms were *Str. faecalis* or *Candida* spp., which are intrinsically resistant to both of these antibiotics. The first 50 patients were checked for absorption of these drugs from the bladder, but detectable amounts of kanamycin and colistin in their blood were not found. Since Harper and Matz (1976) demonstrated that kanamycin-colistin solution frequently caused severe reactions in the rat bladder, a trial using no bladder instillation after catheterisation was carried out. This trial resulted in a much higher (50% increase) incidence of infection during intermittent catheterisation than when kanamycin-colistin was instilled (Pearman, 1979).

Neomycin Sulphate

This was studied in 1969 by Hinman and Belzer, who inserted catheters with sterile precautions into 54 patients prior to renal homotransplantation. The bladder was irrigated with sterile saline and 50 ml of a 1% solution of neomycin sulphate was then left in the bladder for 15 min by clamping the catheter. Immediately after transplantation 75% of the patients who had been given bladder irrigations with 1% neomycin sulphate had sterile urine compared with only 33% of those not irrigated. However, after removal of the catheter there was no significant difference in the incidence of UTI in either group. It is apparent that irrigation with this solution only transiently reduced the incidence of bacterial invasion of the bladder.

Nitrofurazone

Meyers *et al.* (1964) prepared a solution containing 350 mg of nitrofurazone/l and continuously irrigated the bladders of patients at a rate of 30 ml/h. On this regime 11% of their patients with indwelling catheters developed UTI after 5 days and 25% were infected after 10 days. There were 3 problems in using this solution. Firstly, a significant proportion of potential urinary tract pathogens in the bowel flora such as *Ps. aeruginosa*, most strains of *Proteus* spp., many strains of

Esch. coli and some strains of *Str. faecalis* are inherently resistant to nitrofurazone (Meyers *et al.*, 1964; Truss and Nabert-Bock, 1974). Secondly, 19% of the patients developed gross haematuria. Thirdly, toxic concentrations of the solvent (polyethylene glycol) used to prepare nitrofurazone are absorbed into the circulation (Meyers *et al.*, 1964).

Noxythiolin (Noxyflex)

Noxythiolin has been used as a bladder instillation solution with 50 ml of an aqueous solution (2.5% or 1%) being instilled into the bladder before removal of the catheter (MacFadyen and Simmons, 1968). The 1% solution was found to be as effective as the 2.5% and cases of haematuria were less prevalent with the weaker solution (MacFadyen, 1967). It was reported that the overall incidence of infection using noxythiolin was 13.1%. By comparison, the infection rate was 20% when 0.2% chlorhexidine was used. As the reports of MacFadyen (1967) and MacFadyen and Simmons (1968) indicate that it causes significant haematuria, this would suggest that its use would not be warranted.

Polymyxin B-Neomycin

Martin and Bookrajian (1962) first reported the use of a solution of polymyxin B (200 mg/l) and neomycin (40 mg/l) in saline for the continuous irrigation of the bladder to prevent bacteriuria during indwelling catheterisation. In a controlled study by Meyers *et al.* (1964), the incidence of bacteriuria was 4, 6 and 10% after 5, 10 and 15 days' catheterisation respectively. Thornton and Andriole (1970) (constant irrigation) and Hodari and Hodgkinson (1966) (total drainage) have confirmed the efficacy of polymyxin-neomycin as an irrigation solution. However, Zinner *et al.* (1970) reported that continuous irrigation with decompression using a triple-lumen Foley catheter was necessary to bathe all of the urothelium. Otherwise the bacteria on the urothelium which had not come in contact with the solution could reseed the urine. This, of course, would apply to any irrigation solution used.

Polymyxin and neomycin were selected because both compounds are bactericidal in low concentrations, few potential urinary pathogens are resistant to both antibiotics, and the emergence of strains resistant to both antibiotics is very low (Martin and Bookrajian, 1962). The low incidence of resistance has been confirmed by Meyers *et al.* (1964).

Meyers *et al.* (1964) and Chamberlain and Needham (1976) reported negligible absorption of these antibiotics into the circulation when they were used for irrigating the bladder. Nevertheless, dangerously high concentrations of these toxic antibiotics may be absorbed after the urothelium has been breached by surgery of the bladder or prostatectomy.

Povidone-iodine (Betadine)

Iodine has been used as an effective bactericide for more than a century (Davine, 1873; Sigga, 1957). Two problems with its use as an antiseptic have been its high chemical activity and its propensity to cause an allergic reaction. These difficulties have been largely overcome by the use of a complex of the polymer polyvinyl pyrrolidone and iodine (povidone-iodine) (Sigga, 1957). Povidone-iodine is water soluble, chemically stable and does not cause reactions in patients sensitive to elemental iodine on skin patch testing (Shelanski and Shelanski, 1956). It has not been associated with the emergence of resistant strains of bacteria (Houang *et al.*, 1976), which suggests that its use in catheterisation procedures would be advantageous in controlling nosocomial infections. However, the animal studies of Harper and Matz (1976) have shown severe erosive reactions when povidone-iodine was perfused in rat bladders.

Discussion

An irrigating solution for topical treatment of a bladder infection can be selected according to the sensitivity of the micro-organism infecting the bladder. However, the selection of an instillation solution for use in preventing infection caused by intermittent catheterisation is difficult because of the wide ranging species of micro-organisms that can be expected, and no one solution appears to cover this situation. The erosive side effects which have been reported in the literature make the selection more restrictive in cases where prolonged intermittent catheterisation procedures are envisaged, as in the case of spinal cord injured patients.

The studies on water and saline (Harper and Matz, 1975, 1976), and on polymyxin, framycetin, neomycin and EDTA/lysozyme (Harper, 1979) showed them to be the least erosive solutions when tested in rat bladders. Also, no reports of these solutions causing clinical signs of haematuria have been cited in the literature. All of the other solutions discussed in this review have produced severe erosive reactions when perfused in rat bladders and the clinical reports of haematuria caused by chlorhexidine were confirmed.

Thus, while not all solutions have had reports of clinical erosive reactions, one should be aware of the possible erosive side effects of any instillation solution being considered for prolonged use. The successful use of EDTA/lysozyme, as reported by Goldschmidt *et al.* (1972), may have been due in part to the wash-out effect with the volume of solution and method of application described. However, the results of *in vitro* tests using undiluted pooled urine (Harper, 1979) demonstrated the inhibiting action of urine on this solution. This could be further affected over a 6-h period when it was being continually diluted by urine entering the bladder if 25 ml volumes were used, as suggested in other regimens to reduce overdistension. A suggested regimen of alternately using 2 solutions 6-hourly may increase the range of bacteria which the instillations could cover. One pair of solutions worth considering is polymyxin/neomycin (due to low side effects) and EDTA/lysozyme at twice the concentration previously used to overcome the dilution factor. The effect of the EDTA may also enhance the action of the polymyxin/neomycin by weakening the cell walls of the residual bacteria in the bladder after each alternate catheterisation. A microbiological monitoring system on the local environment of the hospital or clinic concerned may also aid in adjustments to the solutions used. Selection could then be made as to the composition of the mixtures used on a 3-monthly cycle with a view to reducing the prevalence of resistant strains in the particular hospital environment.

It is concluded that the use of instillation solutions in intermittent catheterisation procedures has proved beneficial in reducing infection caused by this procedure, and incorporation of other supplementary combinations in the regimen may further reduce infection.

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Combined Surgery and Adjuvant Chemotherapy with High Dose Methotrexate and Folinic Acid Rescue (HDMTX-CF) for Infiltrating Tumours of the Bladder

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Summary—Of the 44 patients seen during the period January 1974 to March 1979 with category T3 or T4 bladder cancer, 33 were treated by partial or total cystectomy followed by adjuvant chemotherapy with high dose methotrexate and folinic acid rescue (HDMTX-CF), with a survival rate at 2 years of 90%. Two patients were given palliative treatment with HDMTX-CF alone; one of them is alive and disease-free after 39 months.

A study of recent publications on the treatment of infiltrating tumours of the bladder shows that this disease is too frequently treated as a local condition with local treatment, *i.e.* surgery or radiotherapy or a combination of both. In fact, patients suffering from infiltrating bladder cancer should be considered as having a systemic disease, or at least a disease that has the potential for systemic involvement. It follows that if the therapeutic objective is cure, therapy should contain a systemic element.

This hypothesis assumes clinical importance when the results of local treatment alone of infiltrating bladder cancer are considered. In a review of the English language medical literature, Jewett (1970) showed that the results of total cystectomy alone were poor, the 5-year survival rate for patients with category T3 and T4 lesions being 9 and 3% respectively. The 5-year survival rate following radiotherapy as primary treatment was little better, being 19 and 1% for patients with T3 and T4 tumours respectively (Kuohara *et al.*, 1965; Cuccia, 1969). Other reports by Morrison and Deeley (1965), Prout *et al.* (1970), Van der Werf Messing (1975), Miller (1977), and Ellingwood *et al.* (1979), using surgery combined with radiotherapy, have shown improved results but there is clearly considerable scope for improvement and a satisfactory approach to the treatment of infiltrating bladder tumours has yet to be found. In this study which concerns patients with category T3 and T4 lesions we have used adjuvant chemotherapy with high dose methotrexate and folinic acid rescue in an attempt to improve on these results.

Chemotherapy

Interest in the potential of chemotherapy in the treatment of bladder cancer is increasing, but this field is as yet inadequately studied and the role of chemotherapy is ill-defined. 5-Fluorouracil has been one of the most extensively studied single agents but results in terms of response rates and duration of response are not encouraging (Prout, 1968), are difficult to interpret and follow-up has generally been of short duration. This is also the case for Adriamycin (O'Bryan, 1973) and cis-platinum (Yagoda, 1976). Furthermore, combinations of these agents have not dramatically improved response rates, while host toxicity has been increased, often to unacceptable levels (EORTC Urological Group B, 1977).

Methotrexate was first studied in bladder cancer by Burn *et al.* (1966) who administered the drug by intra-arterial infusion over 24 h at doses of 40 to 50 mg. Responses were observed in 8 of 12 patients. Altman *et al.* (1972) treated 11 patients with advanced bladder cancer using methotrexate 20 to 40 mg intravenously every 1 to 4 weeks. Tumour mass decreased in 4 patients and 1 patient had an apparent complete response on cystoscopic examination. A 26% response rate was reported by Hall *et al.* (1974) using 50 to 100 mg methotrexate i.v. every 2 weeks in 42 patients with advanced bladder cancer. Finally, a 56% response rate was reported by Turner *et al.* (1977) using methotrexate 100 mg intramuscularly every 2

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weeks. These results clearly demonstrate that methotrexate is active as a single agent against advanced bladder cancer.

In choosing a schedule of methotrexate we have based our approach on the experience of Altman *et al.* (1972) but have used higher doses of 1 to 2 g with folinic acid rescue, in order to overcome natural or acquired resistance to the drug. Extensive clinical and pharmacological studies (Isacoff *et al.*, 1976; Bleyer, 1978) have now shown that provided certain precautions are observed, as described below, and patients satisfy various pre-treatment criteria, methotrexate is well tolerated and has a low incidence of toxic effects when compared with other cytotoxic drugs. The toxicity of methotrexate to normal organs, especially the gastrointestinal tract and bone marrow, is largely a function of the duration of exposure: the greater the duration of exposure the more severe the toxicity (Goldie *et al.*, 1972). Methotrexate is primarily detoxified by renal excretion and it is essential that patients have adequate renal function.

Patients and Methods

We have observed the classification of the Union Internationale contre le Cancer (UICC, 1978) in this study which concerns patients with category T3 or T4 transitional cell bladder cancer lesions. The N category was based upon clinical examination, radiography, including lymphography, urography and CT scan, and the M category was determined by clinical examination, radiology of the thorax and bone scan. Liver scans were also carried out if clinically indicated.

Pre-Treatment Investigations

Prior to and 12 days after administration of HDMTX-CF, total WBC and platelet counts were determined. Minimum pre-treatment leucocyte and platelet levels were 3000 and 100,000 respectively. Serum creatinine determinations were made immediately prior to treatment and 24 h later. Minimum pre-treatment creatinine levels were 1.2 mg% in females and 1.5 mg% in males. If there was a rise of 50% or more in the serum creatinine at 24 h, the dose and the duration of folinic acid rescue were increased.

Surgery

Total cystectomy was done in the 5 patients with T3b tumours and the 3 with T4 tumours, and partial cystectomy in the 25 patients with T3a tumours (Table 1). We were concerned as part of our study to determine whether high dose chemotherapy permitted conservation of some of the bladder in patients with T3a tumours and therefore did a partial cystectomy in these patients if the bladder trigone was intact, if only one ureteric orifice was involved and if that ureter could be reimplanted into healthy bladder, and if any lymph node involvement was homolateral and regional (N1).

Table 1 Distribution of Patients According to TNM Classification, Histological Grading and Treatment

Group	*Treatment*	*No. of patients*	*G**
A = T3a, No, Mo	Partial cystectomy followed by HDMTX-CF 6 courses	20	G2 = 16 G3 = 4
B = T3a, N +, Mo	Partial cystectomy + Regional lymphadenectomy followed by HDMTX-CF 9 courses	5	G2 = 2 G3 = 3
C = T3b, No, Mo	Total cystectomy followed by HDMTX-CF 9 courses	3	G3 = 3
D = T3b, N +, Mo	Total cystectomy followed by HDMTX-CF 12 courses	2	G2 = 1 G3 = 1
E = T4a, No, Mo	Total cystectomy followed by HDMTX-CF 12 courses	3	G3 = 3
F	HDMTX-CF palliative: 1 patient: T3b, No, Mo 24 months with HDMTX-CF 1 patient: T4, N +, M 11 months (died)	2	G3 = 2
Total	33 patients: Cystectomy + HDMTX-CF 2 patients: HDMTX-CF	35	

N.B.: HDMTX-CF was initially 1 g and all courses thereafter 2 g.
G*: histopathological grading after surgery of biopsy (Group F alone).

Administration of HDMTX-CF

Methotrexate (1-2 g) was given by i.v. infusion in 1 litre of saline over 6 h. Six hours after this infusion, folinic acid (9-12 mg), was given i.v., i.m. or orally every 6 h for 8 doses. Urinary pH was made alkaline prior to the methotrexate infusion by administration of oral sodium bicarbonate. Patients were instructed to drink a minimum of 3 litres of fluid/24 h, starting 24 h before the methotrexate infusion and continuing for 3 days thereafter to maintain a urinary output >2.5 l/24 h.

Patients gargled every 3 h for 2 days following the infusion with the following solution:

Polymycin B	2.25 mg
Neomycin	166.25 mg
Bacitracin	215.00 mg
Aurantii Corticus Syrup to 1 litre	

In addition, patients were instructed to swallow 3.5 ml nystatin drops (100,000 iu/ml) or to chew a tablet of nystatin (500,000 iu) every 3 h. Where nausea occurred an anti-emetic was prescribed. Where there was vomiting, hydration was maintained by infusion of i.v. fluids. Chemotherapy was commenced 6 weeks after cystectomy and continued at 3-weekly intervals for a minimum of 6 months. Where treatment was palliative it was continued as long as it was beneficial to the patient.

Follow-up

In addition to the pre-treatment investigation described, all patients underwent full clinical examination before and after each HDMTX-CF course. Cystoscopy was performed every 3 months for the first year, every 6 months for the second year and thereafter annually or, alternatively, on reporting haematuria. Those patients treated by total cystectomy had follow-up CAT scans of the pelvis every 6 months. Radiological assessment comprised intravenous urography and chest X-ray every 6 months for 1 year and thereafter annually. Bone scans were done annually.

Table 2 Survival of 33 Patients with T3 or T4 Bladder Tumours Treated by Partial or Total Cystectomy + HDMTX-CF

Follow-up (months)	*No. of patients*	*No. surviving*	*% survival*
> 12	31	31	100
> 24	20	18	90
> 36	10	6	60

Results

Thirty-three patients with category T3 or T4 transitional cell lesions received adjuvant chemotherapy with HDMTX-CF following partial or total cystectomy. A further 2 patients received HDMTX-CF as palliative therapy only.

The TNM classification before surgery and the histopathological grading after surgical treatment of the 35 patients is shown in Table 1.

Table 2 shows the actuarial survival rate for the 33 patients with category T3 or T4 lesions treated by partial or total cystectomy followed by adjuvant chemotherapy with HDMTX-CF. All 31 patients were alive and disease-free with a follow-up of at least 12 months and 18 of 20 patients were alive and disease-free at 24 months. Of 10 patients with a follow-up of > 36 months, 6 are alive and disease-free.

Of the 2 patients treated palliatively, one patient with T3b, No, Mo disease is alive and disease-free after 39 months. The other patient with T4, N4, M1 disease died of metastatic disease at 11 months.

The causes of death are summarised in Table 3.

Table 3 Deaths and/or Complications in 35 Patients

Group	*Total number*	*Deaths—Complications*	*Surviving*
A = T3a, No, Mo	20	0	20
B = T3a, N +, Mo	5	(17m)$^+$: death from generalised metastases (21m): cerebral metastases (deceased)	2
C = T3b, No, Mo	3	(33m): deceased following myocardial infarction	2
D = T3b, N +, Mo	2	0	
E = T4a, No, Mo	3	(27m): pathological fracture + embolism (deceased)	2
F = palliative	2	(11m): deceased	1
	35	+ (survival between beginning of HDMTX treatment and death)	30

Complications

Only one complication was observed in this series, namely an ulcerative stomatitis associated with bullous dermatitis in a patient with slight renal impairment (creatinine 2.20 mg%) following i.v. infusion of methotrexate 1 g. Administration of folinic acid 12 mg i.m. every 6 h, along with mouthwash as formulated above and nystatin drops, relieved the symptoms within 48 h.

The fact that we encountered no bone marrow toxicity is, we believe, due to the meticulous observation by patients and nursing staff of the following precautions: high fluid intake, alkalinisation of the urine with bicarbonate water and regular mouthwashes. As we have mentioned, it is essential that patients treated with HDMTX satisfy various pre-treatment requirements, in particular that of adequate renal function. A rise in serum creatinine of 50% or more 24 h after methotrexate infusion necessitates immediate intervention with increased doses and duration of folinic acid rescue and frequent mouthwashes.

Discussion

Our results, using HDMTX-CF as adjuvant therapy to partial or total cystectomy for patients with T3 or T4 bladder tumours, confirm the activity of methotrexate against bladder cancer. The absence of local tumour recurrence in the bladder after partial cystectomy is particularly noteworthy.

After a follow-up of 12 months all 31 patients with category T3 or T4 lesions were alive and disease-free. Of 20 such patients with a follow-up of 24 months or more, 18 were alive and disease-free and 6 out of 10 patients are alive and disease-free with a follow-up period exceeding 36 months. The 12-month and 24-month survival rates are therefore 100 and 90% respectively.

Of the 23 patients with category T3 lesions without nodal involvement (20 T3a, No, Mo and 3 T3b, No, Mo), one died from myocardial infarction. Thus 22 out of 23 patients are alive (and disease-free) with a minimum follow-up of 12 months and a median follow-up of 30 months.

If we consider all of the T3 patients, there were 3 deaths out of 30 patients. One patient, T3, N+, Mo, died at 17 months of generalised metastatic disease; one patient T3, N+, Mo, died at 21 months of cerebral metastases and one patient, T3, No, Mo, of myocardial infarction.

While it is too early to draw definitive conclusions from this study, our results at present are superior to those reported by Jewett (1970), by Cuccia (1969) and by Kuohara *et al.* (1965) for surgery or radiotherapy alone, and are also superior to the results reported by Carter and Wasserman (1975) for surgery combined with radiotherapy.

We are optimistic that our results (90% survival at 2 years) will eventually prove superior to those of Van der Werf Messing (1975) for irradiation followed by cystectomy, where the 3-year and 5-year survival rates were 50% for patients classed T3, N×, Mo operable, those of Miller (1977) where a 5-year survival rate of 46% was reported for patients with category T3 lesions treated by pre-operative irradiation and cystectomy, and those of Ellingwood *et al.* (1979) where a 54% actuarial survival was reported following post-diversion pre-cystectomy irradiation for patients with category T3 lesions.

In conclusion, HDMTX-CF as adjuvant therapy to partial or total cystectomy for patients with category T3 or T4 lesions appears to be highly effective in preventing recurrence and prolonging survival. Treatment was well tolerated with a low incidence of toxic side effects. We now intend to use HDMTX-CF pre-operatively and post-operatively in patients with infiltrating tumours of the bladder in an attempt to improve these results.

Addendum

In the 6 months that have passed since making this preliminary analysis of our results, there have been no further recurrences or deaths.

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A Phase 2 Study of Cis-platinum in Patients with Recurrent Bladder Carcinoma

The London and Oxford Co-operative Urological Cancer Group*

Report prepared by Chemotherapy Sub-Committee†
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Summary—A series of 27 patients with measurable metastases from primary carcinoma of the bladder received cis-platinum 50 mg/m^2/3-weekly. Twenty-six per cent (32% if patients receiving only one injection are excluded) responded for a median of 4 months.

Although combination chemotherapy, when compared with single agent chemotherapy, has been clearly shown to increase the incidence of long-term cure in patients with testicular teratoma, Hodgkin's disease, acute myeloid luekaemia, acute lymphoblastic leukaemia and other childhood malignancies, this is unfortunately not the situation in patients with carcinoma of the bladder.

In carcinoma of the bladder there has been a dichotomy between the chemotherapy experiences in America and European centres. In America, cis-platinum has stood out as the most successful single agent producing measurable response in 30 to 40% of patients (Yagoda *et al.*, 1976; Merrin, 1978; Soloway, 1978). There were early encouraging reports of better results when Adriamycin and 5-fluorouracil or Adriamycin and cyclophosphamide were combined with cis-platinum (Sternberg *et al.*, 1977; Williams *et al.*, 1981), but there is little evidence that these combinations have improved on the results achievable with cis-platinum alone, though it has been clearly demonstrated that toxicity is substantially worse (Yagoda, 1981). In European centres, because of the non-availability of cis-platinum, methotrexate (Hall *et al.*, 1974; Turner *et al.*, 1977; Turner, 1981) or a combination of Adriamycin and 5-fluorouracil (Cross *et al.*, 1976) have been the most frequently used treatments. This paper reports the first results from the use of cis-platinum in Britain and compares them with those achieved from methotrexate.

Patients and Methods

Patients with histologically proven carcinoma of the bladder and measurable disease outside any radiotherapy field and having had no prior chemotherapy were considered for entry into this trial. Patients with severe cardiac or renal disease were excluded. A normal blood count and platelet count and adequate renal function with creatinine clearance greater than 50 ml per min were required. The dosage of cis-platinum was 50 mg/m^2 given as an intravenous push after the patient has been hydrated with 1 litre of dextrose saline over a period of 5 h. Following the treatment, hydration was continued until vomiting had stopped. This was usually within 5 to 6 h but should it not have stopped, hydration was continued at the rate of 3 litres every 24 h. Treatments were repeated at 3-weekly intervals and continued for as long as there was no evidence of disease progression.

Criteria for Response to Treatment (Adapted from Yagoda, 1981)

Complete response (CR) required complete disappearance of all evidence of clinical, radiological and biochemical metastases.

Read at the 36th Annual Meeting of the British Association of Urological Surgeons in Liverpool, June 1980.

Partial response (PR) was defined as greater than 50% reduction in the sum of the products of the dimensions of measurable metastases for more than 4 weeks.

Minimal response (MR) was defined as any unequivocal shrinkage of measurable metastases which was less than 50% or major reduction of symptoms for at least 4 weeks.

Results

There were no complete responses. A disappointing 26% of the patients showed evidence of partial response (Table 1); however, it is difficult to compare the results of this study with others which report on the basis of evaluable patients only. Amongst the patients in this study there were several with extremely advanced disease, including one with brain metastases, and these could not be properly evaluated as they only survived long enough to receive a single dose of drug. After exclusion of these the response rate (32%) approximated to that reported in other studies. Metastatic lymph nodes (Fig. 1) was the most frequent site of disease to show response and primary bladder and bone metastases the least frequent (Table 2).

The most striking effect of this treatment was the rapidity of response. All patients who responded did so within 4 weeks. However, the duration of response was short. One patient, treated at the beginning of the study before we had adequate supplies of cis-platinum, had almost complete disappearance of disease after the first treatment and then, since no further drug was available, was left untreated and showed recurrence within 4 weeks. However, on average the duration was 4 months and the longest response was 9 months. The most impressive response was in a patient with massive hepatic and supraclavicular node metastases 2 to 3 cm in diameter. After 3 treatments he became mobile from being bed-bound, the supraclavicular mass disappeared and there was almost complete disappearance of the palpable liver. At 6 months disease recurred and the patient rapidly died.

Lung metastases in this series do not seem to

Table 1 Summary of Cis-platinum Study in Bladder Cancer

	N	*% PR*	*% PR+MR*	*% alive at 6 months*
All cases	27	26	52	33
≥2 doses of drug	22	32	64	41

PR = Partial response.
MR = Minimal response.

Table 2 Response of Recurrent Bladder to Treatment with Cis-platinum by Site of Disease

	N	*% PR*	*% PR+MR*
Brain and liver	2	50	50
Lung	13	23	38
Lymph nodes or lymphoedema	10	50	90
Primary bladder tumour*	13	8	31
Bone	8	0	38
Soft tissue wound recurrence	2	0	100

*All except one patient had had previous radiotherapy to the bladder.

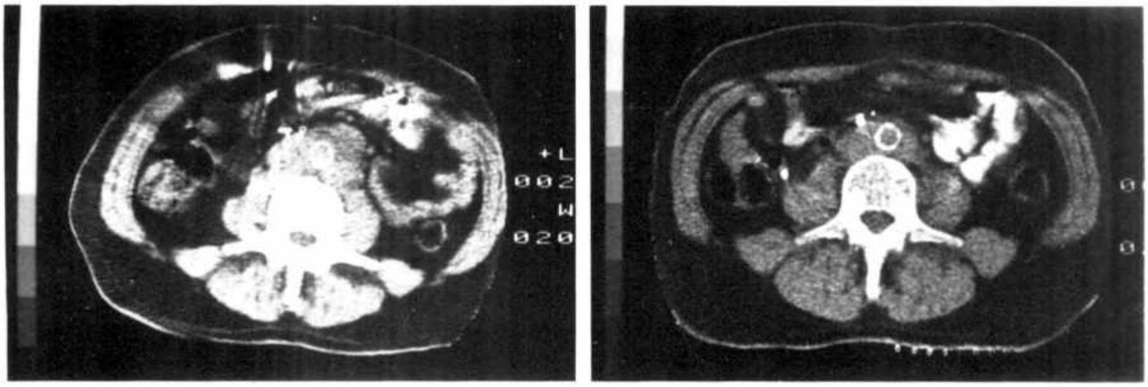

Fig. 1 CT scans of para-aortic region in patient with lymph node metastases from carcinoma of the bladder (a) prior to and (b) 3 months after 4 doses of cis-platinum.

respond as well as in other reported series, or from our own experience using methotrexate. However, Figures 2a and b show the pre- and post-treatment X-ray of one patient who did respond for 6 months.

The most frequent side effect of treatment was vomiting, which occurred in all patients. For most of them it lasted about 2 to 3 h, starting 1 to 2 h after they had received the drug. The most serious complication was renal failure, which occurred in 3 of the non-responding patients terminally. As they all had pelvic tumours and had had previous radiotherapy, it was impossible to be certain that the renal failure was due to renal toxicity of drug or progression of tumour.

Discussion

The response rate of recurrent bladder carcinoma to treatment with cis-platinum reported in this study confirms that cis-platinum is an active drug. Compared with our previous experience, it is better than Adriamycin and bleomycin (Turner *et al.*, 1979) but not as good as methotrexate (Table 3), which possibly has greater activity in patients with lung metastases than cis-platinum but slightly less against metastatic lymph nodes. The lower incidence of side effects from methotrexate make it more suitable as a palliative treatment for use in older patients with bladder cancer.

However, for the future, to improve on these results it will be necessary to find ways of combining platinum and methotrexate. So far, this has been extremely difficult because of the renal tubular toxicity of cis-platinum interfering with excretion of methotrexate. The severity of symptoms reported from the combination of methotrexate and cis-platinum in head and neck cancer precludes the use of this combination in bladder cancer until safer ways can be found for monitoring the drug levels.

Table 3 Comparison of Results with Methotrexate and Cis-platinum

Site of disease	*Methotrexate**		*Cis-platinum*	
	N	*%PR*	*N*	*%PR*
Lung	13	69	13	23
Lymph node	15	17	10	50
Bone	15	33	8	0
Other	42	25	17	12
Median duration of response in responder	6 months		4 months	

* Data from Turner (1981).

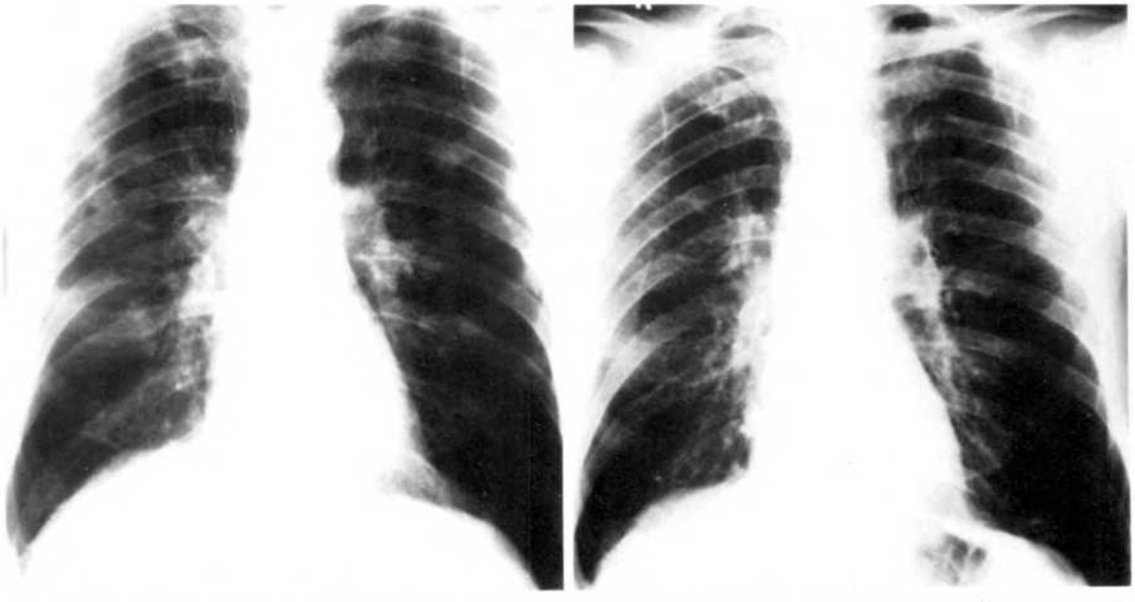

Fig. 2 (a) Chest X-ray of patient with lung metastases from carcinoma of the bladder. (b) Same patient after 5 doses of cis-platinum.

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Synthesis of ABH Blood Group Substances in Bladder Tumours

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Summary—A specific red cell adherence test which can detect the cell surface ABH blood group antigens was performed on formalin-fixed frozen sections of 38 bladder tumours. In 27 tumours decreased glycosyltransferase activity was suggested, but the site and the degree of the blockade did not seem to be identical in every tumour.

Blood group A and B tumours could be grouped into 4 types according to the presence of these 3 isoantigens. One group which showed A or B but no H activity (Type I) consisted only of grade 1, superficial tumours. All of the invasive tumours belonged to other types.

For blood group O tumours no clear-cut correlation could be found between malignancy of the tumour and the presence of H activity.

Eight of 22 grade 2 or 3 tumours and 9 of 21 invasive tumours retained the isoantigen, which seemed to invalidate the use of this test as a predictive indicator. Only where blood group A or B patients were concerned, and the presence of H activity was regarded as abnormal as well as the absence of A and B, could all grade 2 or 3 tumours and all invasive tumours be detected by this test.

The natural history of the bladder tumour is so variable that a means of identifying tumours with highly malignant potential is desirable. Recently the specific red cell adherence (SRCA) test, which can detect the cell surface ABH blood group (BG) antigens, has received considerable attention in this regard (Catalona, 1980). ABH BG antigens, normally expressed on epithelial cells, are absent on the cells of most high grade tumours, and a direct correlation has been reported between the absence of these antigens and the likelihood of invasion and metastasis (Davidsohn *et al.*, 1973; DeCenzo *et al.*, 1975; Kato, 1977; Bergman and Javadpour, 1978; Lange *et al.*, 1978; Emmott *et al.*, 1979; Richie *et al.*, 1980). Those authors used paraffin-embedded tissues and did not comment on relationships between A, B and H antigens. H substance is a precursor of both A and B substances and is also present on BG O erythrocytes (Watkins, 1972), so that its presence or absence will suggest which step of synthesis of BG substances is affected in malignant tissues. In this study these aspects were investigated with the modified SRCA test (Ishiyama, 1979).

Material and Methods

The series consisted of 38 specimens obtained by transurethral resection (TUR), cystectomy or autopsy at our hospital between 1976 and 1979. Only transitional cell carcinoma was examined. The age of the patients ranged from 29 to 82 years (average 62 years). Nineteen patients were BG A, 4 were BG B, 4 were BG AB and 11 were BG O. Five of these 38 patients had received radiation or chemotherapy prior to surgery.

The modified SRCA test was performed as follows. The tissues were fixed in neutral 10% formalin, embedded in 10% gelatin, quickly frozen at −80°C and stored. Materials for SRCA included the antisera anti-A and anti-B from Ortho Laboratories. Detection of H substance was done with extracts of Ulex europeus seeds prepared by homogenisation and centrifugation at 15,000 rpm for 30 min in place of antisera. The indicator erythrocytes were outdated blood bank cells washed 3 times and resuspended to give 2% suspension in phosphate buffered saline (PBS), ph 7.4. All reactions were made at room temperature for BG A and B substances, but at 4°C for H substance.

Frozen sections 7 μm thick were mounted on glass slides which were dipped in either 0.1% Tween 80 or physiological saline for about 1 min. The former was used only for A and B substances to diminish non-specific reactions. The slides were placed in a moist chamber and covered with appropriate antisera for 15 min or with Ulex extract for 60 min. Then the slides were washed in 3 changes

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of PBS for 15 min each and incubated with indicator erythrocytes. After 15 (BG A or B) or 30 min (BG O), they were turned upside down and placed carefully on wooden applicators in Petri dishes filled with PBS. The slides were left in this position for 5 min so that the unattached indicator cells would fall off. Then they were moved aside to an area of clear buffer and examined under the microscope while inverted. To make the final product permanent these slides were dried at 60°C and stained with benzidine, nitroprosside and neutral red. In the most recent experiment they were fixed by adding glutaraldehyde to the dishes and stained with hematoxylin and eosin as usual.

The results of the reaction were graded arbitrarily from negative to very strong adhesion (+ + + +), based on the intensity of erythrocyte packing. We considered (+ +) and above as positive for antigen. The results of the SRCA test was recorded as positive when 70% or more of the area was antigen positive, and recorded as negative when 70% or more was antigen negative. Each specimen was tested for the presence of all 3 BG substances. Reagent controls were the same as those described by others (Bergman and Javadpour, 1978). On each slide normal urothelium, endothelium and erythrocytes served as built-in positive controls, whereas muscle and connective tissue served as built-in negative controls.

Results

The results of the SRCA test for 23 BG A and B tumours could be grouped into 4 types (Table 1):

Type 1 Five tumours were positive for A or B and negative for H substance. All were grade 1 and superficial (Fig. 1).

Type 2 Eight tumours were positive for A or B and also positive for H (Fig. 2). Two tumours were grade 1, 3 were grade 2, and 3 were grade 3. Four tumours were superficial and 4 were invasive.

Type 3 Four tumours were negative for both A and B but positive for H (Fig. 3). All were grade 2 and invasive.

Type 4 Six tumours were negative for all 3 substances. One was grade 1, 3 were grade 2 and 2

Table 1 Correlation of SRCA and Pathological Grade and Stage of Bladder Cancer in 23 BG A and B Patients

SRCA		*No. of pts.*	*Grade*			*Stage*		
A or B	*H*		*1*	*2*	*3*	$\leq T_1$	T_2	$T_3 \leq$
+	–	5	5	0	0	5	0	0
+	+	8	2	3	3	4	2	2
–	+	4	0	4	0	0	1	3
–	–	6	1	3	2	1	1	4

+ : Positive – : Negative

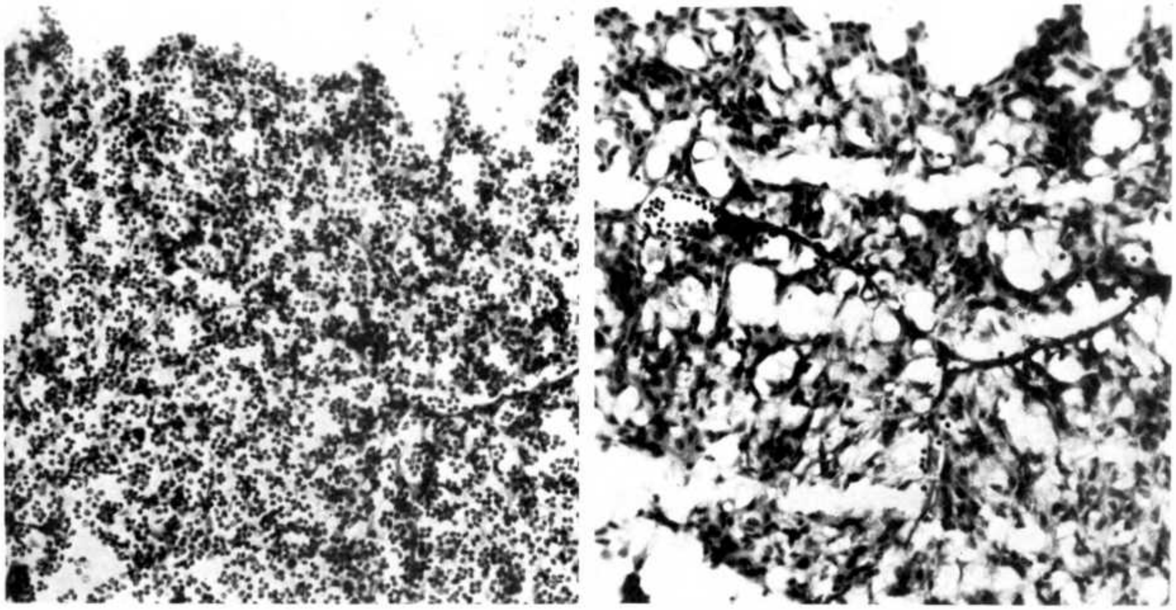

Fig. 1 Isoantigenic activity of a blood group B bladder tumour (grade 1, T1). B activity was found (a), but no H activity (b) (H and E × 100).

were grade 3. One was superificial and 4 were invasive.

No incompatible BG substance was detected in any tumour.

All 11 BG O tumours were negative for A and B. One of 5 superficial tumours and 4 of 6 invasive tumours were positive for H. Three of 6 grade 1 tumours and 2 of 5 grade 2 tumours were positive for H (Table 2).

Of 4 BG AB tumours 2 were negative for all 3 substances, 1 was positive for A and B but negative for H and 1 was positive for A but negative for B and H (Table 3).

Eleven of 16 grade 1 tumours, 5 of 15 grade 2, 3 of 7 grade 3, 11 of 17 superficial, and 9 of 21 invasive tumours were positive for the BG antigen identical to that present on the isologous erythrocytes. Three of 6 metastatic tumours and 3 of 5 irradiated tumours were SRCA positive. In 18 cases antigen positive and negative areas were demonstrated side by side within the same field.

Table 2 Correlation of SRCA and Pathological Grade and Stage of Bladder Cancer in 11 BG O Patients

SRCA	*No. of*	*Grade*			*Stage*		
H	*pts.*	*1*	*2*	*3*	*≤T_1*	*T_2*	*T_3≤*
+	5	3	2	0	1	0	4
−	6	3	3	0	4	1	1

+: Positive −: Negative

Discussion

The specificity of ABH BG substances is determined by the terminal carbohydrate residue of glycoproteins or glycolipids. When N-acetyl galactosamine is added to the terminal β-galactose of H substance through the enzyme N-acetyl galactosaminyl transferase(s), BG A substance is synthesised. Similarly, B substance is synthesised by adding galactose to H substance through galactosyl transferase(s) (Watkins, 1972). Thus H is also a precursor of A and B substances.

Normal urothelium of BG A, B and AB subjects shows A, B and both A and B activity

Table 3 Correlation of SRCA and Pathological Grade and Stage of Bladder Cancer in 11 BG O Patients

SRCA			*No. of*	*Grade*			*Stage*		
A	*B*	*H*	*pts.*	*1*	*2*	*3*	*≤T_1*	*T_2*	*T_3≤*
+	+	−	1	1	0	0	1	0	0
+	−	−	1	0	0	1	0	0	1
−	−	−	2	1	0	1	1	0	1

+: Positive −: Negative

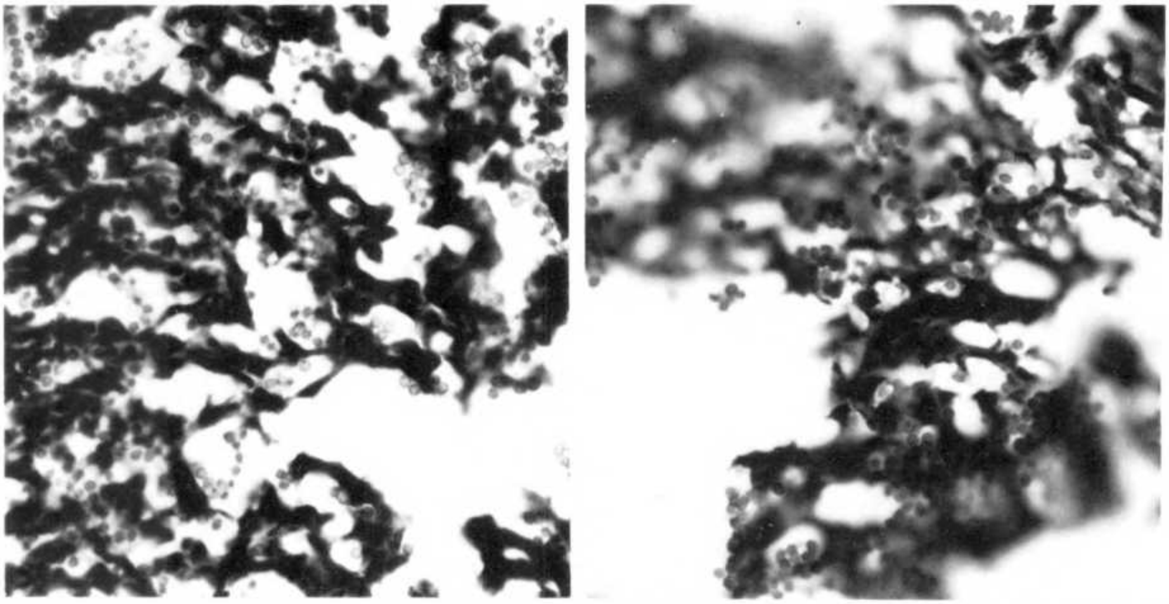

Fig. 2 Isoantigenic activity of a blood group A bladder tumour (grade 2, T2). Both A (a) and H (b) activity was found (H and E ×200).

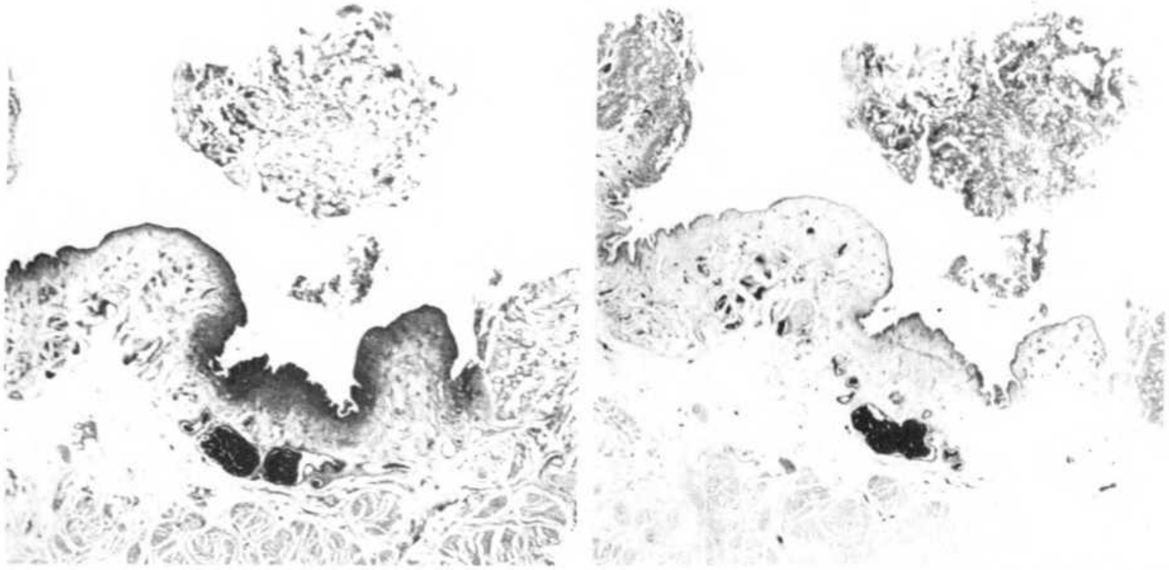

Fig. 3 Isoantigenic activity of a blood group A bladder tumour (grade 2, T2). Antigen-positive area looks dark in this figure. No A activity (a), but H activity (b) was found in tumours. Note the presence of A and absence of H activity in normal urothelium adjacent to tumours (Benzidine stain × 7).

respectively, but little or no H activity. Only the urothelium of BG O subjects shows definite H activity (Ishiyama, 1979).

Recently a direct relationship between the loss of BG substances from malignant urothelium and the potential malignancy has been reported. No invasive malignancy was found among 13 initially superficial bladder tumours with a positive SRCA test, while 8 of 9 SRCA negative tumours developed into invasive stages during 5 to 14 years' follow-up (DeCenzo *et al.*, 1975). In another series the incidence of invasive tumours among 37 superficial bladder tumours with positive and negative SRCA tests was 13 and 76% respectively (Lange *et al.*, 1978), but no correlation between the results of the SRCA test and the recurrence rate could be found (Johnson and Lamm, 1980). In a cystectomy series, 31 of 32 invasive tumours showed a negative SRCA test (Richie *et al.*, 1980). Furthermore, BG antigens were absent in metastatic lesions (Davidsohn *et al.*, 1973; Emmott *et al.*, 1979). Similar results indicating the ability of the SRCA test to predict cellular dedifferentiation and invasion have accumulated and the overall accuracy rate was 78% (Johnson and Lamm, 1980).

However, conflicting results have been reported. Kay and Wallace (1961) performed the SRCA test on cell suspensions and found no clear correlation between antigen content and other aspects of tumour behaviour in 60 patients. They obtained positive results from 5 of 17 anaplastic tumours and 3 of 14 metastatic tumours. Alroy *et al.* (1978) also observed that a significant number of invasive urothelial carcinomas were strongly positive for A, B and H antigens. All invasive bladder tumours from 8 patients with prior radiotherapy or chemotherapy showed positive SRCA test results, so that the effect of radiation on the induction of differentiation in tumours was suggested. Only 5 of our 38 patients had received radiotherapy, but 43% of grade 3 tumours, 43% of invasive tumours and 60% of metastatic tumours gave positive SRCA test results, which seemed to invalidate the use of this test as a predictive marker.

These differences might be accounted for, at least in part, by the method used. Paraffin-embedded tissues give inconsistent results for H substances, as recognised by others (Bergman and Javadpour, 1978), so we used gelatin-embedded frozen sections and performed the test at 4°C for H. Our method is unsatisfactory for studying cellular details, but is more sensitive than the original one in detecting A, B and H substances (Fujita and Ishiyama, 1979; unpublished observation). There is also a possibility that the antigenic determinants reacting in our cases are actually "blood group-like" substances. The racial difference may have to be considered as well.

It has been suggested that the process of ontogenesis of a BG carbohydrate chain occurs as a step-by-step elongation and arborisation, and that blocking of such a development and an accumulation of a simpler form occur in the process of oncogenesis (Watanabe and Hakomori, 1976). Thus the genesis of 4 types described for BG A and B tumours may be explained as follows. When H substance is totally converted into A or B substance, no H activity will be detectable (Type 1). When conversion of H is partially blocked or H is produced in excess of glycosyltransferase activities, H activity will appear as well (Type 2). With complete blockade only H activity will be detectable (Type 3). On the other hand, when synthesis of H substance is blocked completely, there will be no ABH activity (Type 4), and when it is blocked incompletely, A or B activity will appear (Type 1). Thus the simultaneous presence of different types in the same tumour may be considered to indicate the progressive loss of glycosyltransferase activities.

If Types 2, 3 and 4 are considered abnormal, all grade 2 and 3 tumours and invasive tumours gave abnormal SRCA patterns. Type 1 contained only low grade and superficial tumours. If the mere presence of A or B is considered SRCA positive, 6 of 15 grade 2 and 3 tumours and 4 of 13 invasive tumours showed positive results.

No clear-cut correlation could be found in BG O tumours between the histopathological grade and stage and the presence of H substance. For BG AB patients, less malignant tumours seemed to have A and B but no H activity, though more experience is needed to draw any conclusions. Of 5 irradiated tumours, the 3 with a positive SRCA test belonged to BG O or Type 1. Thus the effect of radiation could not be demonstrated clearly.

Our results indicate that deletion or inhibition of the glycosyltransferases for the terminal sequences of ABH BG substances occurs frequently in the bladder tumours, though at variable steps and to a variable extent. It seems dangerous to predict the malignant potential of the tumour only from the presence or absence of ABH isoantigens. Only for BG A and B (and possibly AB) patients, and only with the knowledge of the presence of H substance as well as A and B, will the SRCA test become a useful method for discriminating benign from early malignant lesions. We are now correlating the 4 types of BG A and B tumours with the clinical course of the patients.

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Urological Complications of Traumatic Diastasis of the Symphysis Pubis in the Female

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Summary—We report on 2 cases of traumatic diastasis of the symphysis pubis in the female with injury to the soft tissue supports of the bladder neck resulting in urinary incontinence, unnoticed until discharge from hospital.

Injuries to the bladder and urethra are found in 10% of cases of fractured pelvis (Peltier, 1965). The urethra in the adult female is rarely injured because of its shortness and mobility (Williams, 1975; Casselman and Schillinger, 1977). However, when hinge injuries occur which open the pelvic ring, damage can result.

Case Reports

Case 1. A 71-year-old nulliparous woman, previously continent, suffered a road traffic accident and sustained a fractured pelvis with diastasis of the symphysis pubis (Fig. 1) and bilateral fractures of the tibia and fibula. There were no urinary symptoms at that time. An abdominal injury was suspected and a laparotomy performed. The pelvic organs appeared intact and the symphysis pubis was wired together. She subsequently complained of urinary incontinence on standing, without other symptoms. Examination revealed a patulous urethra, without genital prolapse. Subtracted cystometry was normal apart from a detrusor pressure rise of 20 cm of water. No contractions were noted.

Case 2. A 58-year-old primiparous woman was continent until a road traffic accident in May 1975, when she suffered a fractured pelvis with diastasis of the symphysis pubis (Fig. 2) and fractures of the left tibia and fibula. There were no urinary symptoms and at laparotomy no urethral or bladder injury was found. When fully mobilised in October 1976 she complained of stress incontinence and 6 months later an anterior repair was performed with slight improvement for 2 weeks only.

When first seen here 3 months later, she complained of incontinence on effort and on standing up. The urethra was patulous but the bladder neck and base of bladder were well supported. Videocystourethrography demonstrated marked incontinence on standing up and on coughing, without abnormal detrusor pressure rise. Her urethral pressure at rest and on squeezing was 22 cm of water. A colposuspension was performed without improvement. In October 1977 a urethroplasty (urethral narrowing procedure) was performed via the vagina, with improvement for 2 weeks only. Videocystourethrography and urethral pressure measurements were unchanged. Finally a neo-urethra was constructed from an anterior bladder flap (Tanagho, 1976) which improved her continence control so that she now had only occasional episodes of stress incontinence. Her post-operative urethral pressure on squeezing was 31 cm of water. Post-operative videocystourethrography showed a bladder capacity of only 150 ml but a normal pressure rise and some loss of urine on coughing. Voluntary interruption was present and no residual urine remained following voiding.

Discussion

The likely mechanism of incontinence here is disruption of the supports of the bladder neck and

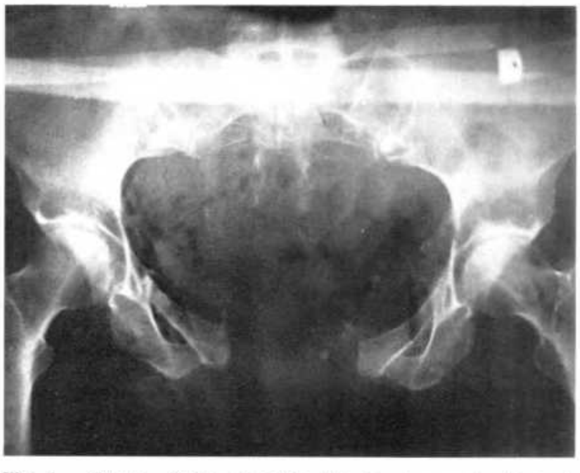

Fig. 1 Case 1. X-ray of pelvis showing traumatic diastasis of the symphysis and fractures of the internal pelvic ring.

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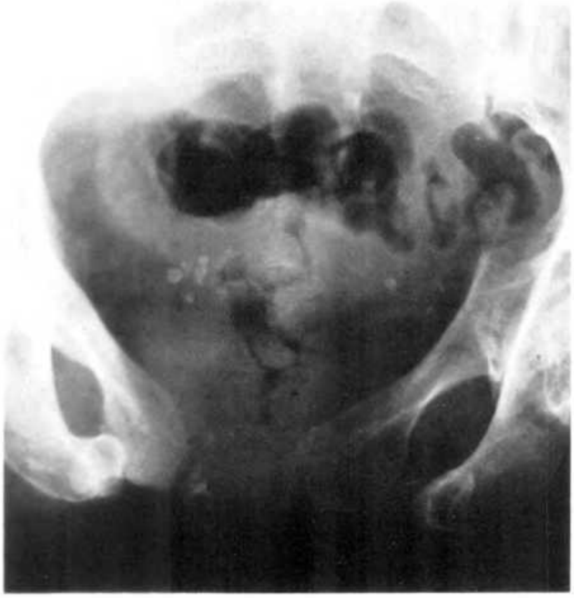

Fig. 2 Case 2. Diastasis of the symphysis pubis.

proximal urethra. These include the posterior pubo-urethral ligaments, pubocervical fascia and pelvic floor musculature. This results in a lowered intra-urethral pressure which is easily surpassed by any rise of bladder pressure, *e.g.* coughing or standing up (Enhorning, 1961). This mechanism is found in other situations where there is symphysial separation, *e.g.* epispadias (Stanton, 1974) and following symphysiotomy for cephalopelvic disproportion in labour (Lawson and Stewart, 1967).

Bladder neck descent and anterior vaginal wall prolapse are not necessarily found with these conditions and therefore conventional surgery to elevate the bladder neck is unlikely to be successful, as confirmed by Case 2. Instead, urethral reconstruction designed to increase intra-urethral pressure is more logical.

Diagnosis of injury to the ligamentous supports of the urethra or bladder neck is unlikely to be made unless specific questions about continence control are asked, especially when signs of injury to the urethra and bladder are absent. Symphysial diastasis in the female should alert the clinician to the likelihood of incontinence. Ideally, urodynamic evaluation should be performed prior to treatment.

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The Diagnosis and Management of Acute Scrotal Conditions in Boys

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Summary—In a consecutive series of 69 boys with an acute scrotal condition, 55% were suffering from torsion of a testicular appendage, 22% from torsion of the testis and the remainder from idiopathic scrotal oedema or epididymitis. The general clinical features and specific scrotal findings in each of these conditions are compared and contrasted.

It is concluded that on clinical grounds alone, torsion of the testis can be excluded in many boys presenting with an acute scrotal condition. The implications for management are discussed.

Acute scrotal conditions are less commonly encountered in boys than in adolescents or adults (Williamson, 1976) but, regardless of the age of the patient, the consensus of published opinion on this subject is that torsion of the testis is the commonest cause of this problem, that this condition can rarely, if ever, be reliably distinguished on clinical grounds from other causes of acute scrotal pain, and hence that all affected patients should undergo urgent scrotal exploration (Jones, 1962; McFarland, 1966; Snyder *et al.*, 1969; McNicol, 1974; Greaney, 1975; Williamson, 1976). These propositions have currently acquired an almost axiomatic status; we have reviewed our experience to test their validity.

Patients

A retrospective review was made of 69 consecutive patients presenting as an emergency with acute scrotal pain to the Sheffield Children's Hospital in the 5 years 1974 to 1978; 78% were seen at presentation by one or other of the authors. Excluded from consideration were 5 boys who presented to out-patients with a history compatible with intermittent testicular torsion; at exploration no abnormalities were found and the diagnosis in these cases can only be conjectural.

Results

Final Diagnosis (Table 1) and *Age Distribution* (Fig.). The number of cases of torsion of a testicular appendage includes 6 who were treated entirely conservatively (*q.v.*). The 4 infant examples of testicular torsion were all neonates, in 2 of whom there was evidence that the incident had taken place pre-natally. All boys with idiopathic scrotal oedema and appendicular torsion were pre-pubertal, whereas 7 out of 11 older boys with testicular torsion were trans-pubertal or post-pubertal.

General Clinical Features (Table 2) The 4 neonates with testicular torsion presented between 16 h and 4 days after the scrotal swelling was noted. They had no obvious symptoms. In older boys the severity of the symptoms and the general constitutional upset was appreciably greater in testicular torsion than in other acute scrotal conditions, and probably accounts for their earlier presentation.

Table 1 Final Diagnosis

	Number	*Percentage*
Torsion of testis	15	22
Torsion of testicular appendage	38	55
Idiopathic scrotal oedema	9	13
Epididymitis	7	10

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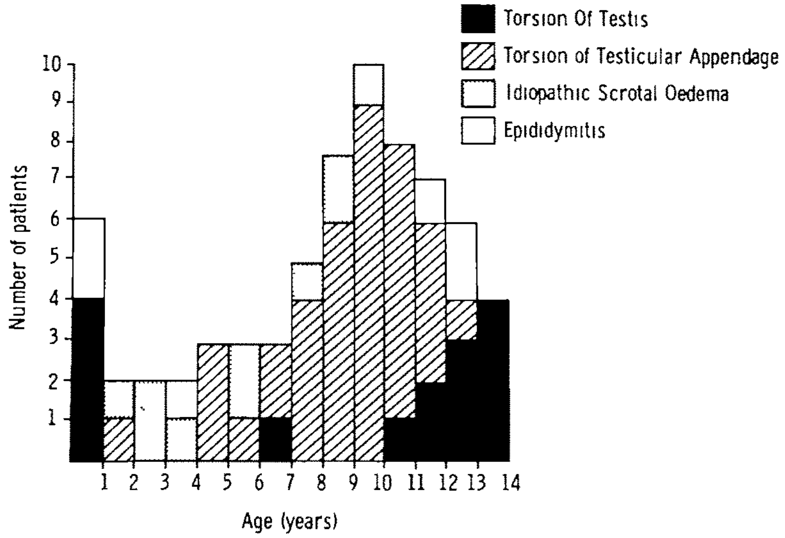

Fig. Age distribution.

Even so, 44% of these cases presented after the first 12 h, although all of them had sought earlier advice from their general practitioner who commonly made a diagnosis of epididymitis.

Findings on Scrotal Examination (Table 3) In cases of torsion of the testis or its appendages, erythema or oedema of the scrotum, or a secondary hydrocele, was only seen when the history exceeded 12 h. The signs as regards the size and tenderness of the testis or its appendages were listed as uncertain when the documentation was inadequate or when a secondary hydrocele or severe scrotal oedema precluded accurate palpation. In 68% of cases of appendicular torsion the lesion was tender and palpably separate from the normal testis. This sign was masked in a few late cases with a secondary hydrocele, and was almost certainly missed in other cases by an inexperienced observer.

Table 2 General Clinical Features

		Torsion of testis	*Torsion of testicular appendage*	*Idiopathic scrotal oedema*	*Epididymitis*
		n = 11*	n = 38	n = 9	n = 7
Duration	0-12 h	6 (56%)	5 (13%)	4 (44%)	1 (14%)
of	13-48 h	—	7 (19%)	3 (33%)	1 (14%)
Symptoms	48 h +	5 (44%)	26 (68%)	2 (22%)	5 (72%)
Pain	None	—	1 (3%)	1 (11%)	2 (28%)
	Mild	2 (18%)	29 (75%)	8 (89%)	4 (58%)
	Severe	9 (82%)	8 (22%)	—	1 (14%)
Onset sudden		10 (91%)	5 (13%)	1 (11%)	2 (28%)
Onset slow		1 (9%)	33 (87%)	4 (44%)	2 (28%)
Uncertain		—	—	4 (44%)	3 (44%)
Abdominal Radiation		3 (27%)	—	—	—
Anorexia/nausea/vomiting		9 (82%)	2 (5%)	1 (11%)	2 (28%)
Loss of sleep		4 (36%)	5 (13%)	—	—
Pyrexia		9 (82%)	5 (13%)	1 (11%)	1 (14%)

* Excludes neonatal cases.

Table 3 Findings on Examination of the Scrotum

		Torsion of testis	*Torsion of testicular appendage*	*Idiopathic scrotal oedema*	*Epididymitis*
		n=15	n=38	n=9	n=7
Side affected	Right	7 (47%)	23 (60%)	3 (33%)	4 (57%)
	Left	8 (53%)	14 (37%)	5 (56%)	3 (43%)
	Bilateral	—	1 (3%)*	1 (11%)	—
Erythema/oedema	Scrotum	10 (67%)	11 (29%)	9 (100%)	1 (14%)
	Groin or perineum	1 (7%)	—	7 (78%)	1 (14%)
Secondary hydrocele		3 (20%)	3 (8%)	—	1 (14%)
Testis	Descended	13 (87%)	38 (100%)	9 (100%)	7 (100%)
	Undescended	2 (13%)	—	—	—
	Normal size	—	26 (68%)	8 (88%)	—
	Enlarged	10 (67%)	—	—	4 (57%)
	Uncertain	5 (33%)	12 (32%)	1 (12%)	3 (43%)
	Non-tender	—	26 (68%)	8 (88%)	—
	Tender	12 (80%)	—	—	4 (57%)
	Uncertain	3 (20%)	12 (32%)	1 (12%)	3 (43%)
Appendix	Impalpable	—	12 (32%)	—	6 (86%)
Testis	Palpable and tender	—	26 (68%)	—	1 (14%)†
	Blue dot sign	—	2 (5%)	—	—

*Sequential bilateral involvement.

†False positive, no testicular appendage found at exploration.

In cases proceeding to exploration, a pre-operative diagnosis was stated in 46 instances with an accuracy shown in Table 4. Torsion of the testis was more commonly diagnosed by the less experienced and torsion of an appendage by the more experienced.

Management

It was invariably the practice to explore the scrotum when testicular torsion was diagnosed or could not be excluded. In the 4 neonates the torsion was supravaginal, but was intravaginal in older boys. In cases of torsion the affected testis was untwisted and fixed to the scrotum regardless of its apparent viability, and the unaffected testis fixed also. In 2 post-pubertal boys a necrotic testis sloughed through the scrotal wound and required secondary excision, but in the remainder a non-viable testis atrophied without further incident. The ultimate fate of the testis was directly related to the length of the history; in 6 where this was less than 12 h, follow-up at 3 months or more revealed a normal testis in 5, and only one with atrophy, whereas in all 9 where the symptoms exceeded 12 h, the testis became atrophic or was excised.

In patients with appendicular torsion undergoing surgery, the lesion was macroscopically haemorrhagic rather than infarcted in 9. With increasing experience, patients with a positive clinical diagnosis of appendicular torsion, and in whom the symptoms were mild or resolving, were managed conservatively. In 6 this management was successful, the symptoms resolving within 2 to 3 days, and follow-up at least 3 months later revealed no scrotal abnormality. The policy failed in one patient whose symptoms persisted for a week, and a haemorrhagic appendage was ultimately excised.

Table 4 Accuracy of Pre-operative Diagnosis

Pre-operative diagnosis		*Post-operative diagnosis*		*Diagnostic accuracy*
Torsion of testis	26	Torsion of testis	14	
		Torsion of appendage	10	54%
		Epididymitis	2	
Torsion of appendage	20	Torsion of appendage	19	95%
		Epididymitis	1	

Eight cases of idiopathic scrotal oedema received no treatment and the scrotal signs resolved within 48 h. One patient with unilateral disease underwent exploration because the underlying testis could not be palpated through unusually severe scrotal oedema. Two infants with epididymitis were treated with antibiotic therapy only; both had a documented urinary tract infection and a known abnormality of their genitourinary tract (one ectopic ureter, one rectourethral fistula). The remainder underwent exploration. All had sterile urine and the aetiology of their condition is unknown.

Discussion

Our findings, which relate to predominantly prepubertal boys, suggest that in paediatric practice traditional views of the diagnosis and management of acute scrotal disease are susceptible to modification.

That torsion of the testis is the commonest cause of the problem is certainly not true in our experience; in this we are in accord with Quist (1956) and Smallman (1960). Even the present series may exaggerate the relative incidence of testicular torsion. The severity of the symptoms and subsequent fate of the testis in this condition makes it likely that most cases will sooner or later reach hospital. The same does not apply to other acute scrotal conditions. In particular, the scrotal findings in appendicular torsion might easily be mistaken by the inexperienced for epididymitis (a diagnosis to which many general practitioners remain addicted) and the subsequent benign course only serves to reinforce confidence in this erroneous assessment. Our finding of a much higher incidence of appendicular torsion than in most previous series is, we suspect, a reflection of the increasing habit of self-referral to hospital in urban populations (*British Medical Journal*, 1979).

The belief that torsion of the testis cannot be reliably distinguished clinically from other acute scrotal conditions is open to question. We find that attention to the general clinical features will suggest, and purposeful examination of the scrotum often clinch, an accurate diagnosis. Torsion of the testis in paediatric practice is a disease of the neonate and the early adolescent; between these extremes it is rare. In older boys constitutional upset is usually marked. Loss of sleep, gastrointestinal upset and abdominal radiation of the pain are almost pathognomonic of this condition. In the acute stage, exquisite tenderness may preclude detailed palpation, but it is usually possible to be certain that it is the testis itself which is the source of the trouble. Torsion of the testicular appendages, while mainly affecting older boys, reaches its peak incidence rather earlier than testicular torsion and, unlike the latter, is principally a disease of the pre-pubertal. Except in a few late cases where a secondary hydrocele masks the signs, accurate palpation of the scrotum is feasible, and reveals a normal testis with the tender, twisted appendage separately palpable, usually in the angle between the upper pole of the testis and the epididymis (Jones, 1962). The "blue dot" sign, where the infarcted appendage is visible through the scrotal skin, is pathognomonic but rare. Idiopathic scrotal oedema affects younger boys than does torsion of the testis or its appendages. Constitutional upset is exceptional and although pain is admitted on direct questioning, the scrotal appearances are the principal feature. Boys with this disease commonly present to casualty departments in early evening because the dramatic appearance of the scrotum only comes to light at bath time. Although erythema and occasionally oedema of the scrotal skin are late features of other acute scrotal conditions, in idiopathic scrotal oedema they are present *per primam*, and extension to the groin or perineum is largely confined to this condition. On palpation it is usually possible to be certain that the underlying scrotal contents are normal. Diagnostically, epididymitis is the odd man out. There is nothing characteristic in the age distribution or the symptomatology, constitutional upset is variable, and on palpation it is not usually possible reliably to distinguish epididymis from testis even if the latter is not involved in the inflammatory process. The diagnosis can only be made with any confidence in the presence simultaneously of a urinary tract infection and a known abnormality of the genitourinary tract which predisposes to retrograde spread of infection along the vas deferens.

In summary we suggest that, with experience, testicular torsion can be positively excluded on clinical grounds in rather more than 50% of boys presenting with an acute scrotal condition. We are, however, hesitant to suggest any modification of the proposition that all boys presenting with an acute scrotal condition should undergo urgent exploration, since any relaxation of this teaching could result in loss of salvageable testes. To any general practitioner we advocate referral of all cases to hospital, to any houseman to seek at once a more experienced opinion, and to any surgeon who sees only a limited number of cases to continue routine and expeditious exploration. It is only to those surgeons who have occasion to deal with any number of these cases that we argue for a more critical approach. Although it must remain the rule that exploration must be undertaken whenever testicular torsion cannot be excluded, it should be rare for the experienced to perform this procedure in cases of idiopathic scrotal oedema. Conversely, no amount of experience will compensate for the difficulty in distinguishing epididymitis from testicular torsion, and most of these cases will inevitably come to exploration. Between these diagnostic extremes lie torsion of the testis and its appendages. When the former is suspected, we would not advocate *urgent* exploration if the history exceeds 24 h, since the chances of salvaging the testis are remote. In this situation, the object of the exercise, if exploration confirms torsion, is fixation of the opposite testis, since the risk of a subsequent contralateral torsion is significant (Ewart and Hoffman, 1944; Adams and Slade, 1958). By contrast, when the history is short, especially under 12 h, the possibility of saving the testis, and the limited time available to do so, provides one of the few justifications for ignoring the customary 4 to 5 hours' starvation before an anaesthetic. Confidence in the surgeon's diagnostic ability materially assists one's anaesthetic colleague's willingness to "bend the rules" in this matter.

When appendicular torsion has been confidently diagnosed, there is no absolute necessity to explore, but bearing in mind the rapid relief of symptoms that excision affords, and the several patients who have a haemorrhagic rather than an infarcted lesion (which might be expected to give more prolonged symptoms), then surgical intervention is the better policy in some cases. An accurate preoperative diagnosis is of technical assistance in that the lesion may be excised through a small incision placed directly over it. Our experience does not provide grounds for routine bilateral exploration; although a pedunculated appendage is very likely to be present in the opposite hemiscrotum (Jones, 1962), it is unlikely to cause any trouble. In cases of torsion of a testicular appendage where the symptoms are mild or resolving, we believe there is a sound case for conservative management.

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Loewenstein-Buschke Tumour of Penis—a Carcinomimic

Report of 24 Cases with Review of the Literature

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Summary—Twenty-four patients with invasive penile condylomatosis (Loewenstein-Buschke tumour) seen over a 10-year period are presented.

The clinical behaviour of the lesions, their pathological nature and response to treatment are reviewed. Their true significance and differentiation from condyloma acuminatum and squamous cell carcinoma are discussed.

It appears that the lesions are not as rare as hitherto believed but are often incorrectly diagnosed as carcinoma.

Invasive penile condylomatosis was first described by Buschke in 1896 and in greater detail by Loewenstein in 1939. Since then scattered reports have appeared in the literature regarding this rare lesion, also referred to as giant condyloma of penis or carcinoma-like condyloma. Only about 90 cases have been described in the literature (Netto *et al.*, 1976). Whilst the nature of the lesion and its clinical behaviour are now clear, its aetiology and relationship to carcinoma remain obscure. Although the lesion has occasionally been referred to as verrucous carcinoma of penis (Ackerman, 1948), no definite proof exists as to its inherent malignancy or its capacity to become malignant.

We report 24 cases of Loewenstein-Buschke tumour of penis seen at this hospital over a 10-year period.

Patients and Methods

Patients with Loewenstein-Buschke tumour of the penis were diagnosed according to the following criteria:

(i) generally large size of the lesions;
(ii) clinical appearance indistinguishable from carcinoma;
(iii) histologically benign appearance confirmed by repeated biopsy;
(iv) demonstration histologically of a growth in depth displacing normal tissues and simulating "invasion", unlike that seen with a true condyloma;
(v) absence of spread to regional lymph nodes in any of the cases;
(vi) non-responsiveness to podophyllin, unlike a true condyloma;
(vii) usually a good response to "conservative" surgery.

These criteria were strictly applied to separate the lesions from condyloma acuminatum and squamous cell carcinoma of the penis.

The age at presentation varied from 18 to 65 years with a mean of 36 years. Two-thirds of the lesions were seen in men under 40 years of age (Table 1). The duration of the disease varied from 1 month to 7 years with a mean of 16 months. Sixteen patients had lesions of less than 1 year's duration at presentation (Table 2).

Seventeen patients showed a slowly progressing clinical course. In 7, however, there was a rapidly proliferating destructive mass simulating carcinoma. A history of frequent extramarital contacts

Table 1 Age at Presentation

Less than 20 years	4
21 to 30 years	7
31 to 40 years	5
41 to 50 years	3
51 to 60 years	3
Over 61 years	2
Total	24

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Table 2 Duration of Disease

Less than 3 months	3
3 to 6 months	5
6 to 9 months	2
9 months to 1 year	6
1 to 2 years	3
2 to 5 years	3
Over 5 years	2
Total	24

was obtained in 10 patients. The tumour appeared to be much more common in uncircumcised males (22 of 24 lesions) (Fig. 1).

The lesions varied in size between 2 and 12 cm, the majority (21) being more than 5 cm in diameter. Most lesions involved only the prepuce and glans. More proximal spread was seen on only 7 occasions (Table 3). Urethral obstruction due to widespread involvement of the urethra was noted in 2 patients (Fig. 2). One lesion was primarily in the perineum and perianal region in addition to involvement of the penis (Fig. 3). Inguinal lymph nodes were palpable in 21 patients but not clinically suggestive of metastatic deposits. Preoperative podophyllin application was tried in 11 patients but without response.

In the initial period most lesions were clinically diagnosed as condyloma acuminatum or carcinoma of penis (Table 4). The latter diagnosis was made in 8 patients who presented with rapidly growing lesions with inguinal lymphadenopathy (Fig. 4). Later in the study better understanding and familiarity with the clinical behaviour of these lesions led to a better clinical assignment of the disease.

All diagnoses were confirmed by repeated pre-

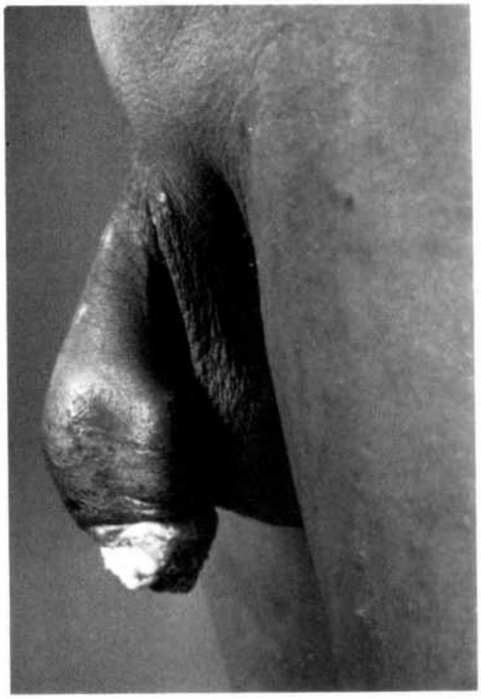

Fig. 1 Loewenstein-Buschke tumour occurring as a subpreputial mass infiltrating the distal shaft of penis.

Table 3 Site of Lesions, Treatment and Follow-up Data

Site	*Number*	*Treatment*	*Number followed up*	*Recurrence*
1. Prepuce + superficial infiltration of glans	3	Circumcision + scraping away of lesions on glans	2	Nil
2. Prepuce + deep infiltrating lesions of glans penis	12	Circumcision + diathermy excision of lesion on glans	8	3 (Further diathermy excision carried out with no recurrence)
3. Infiltrating shaft of penis	5	Partial amputation—3 Total amputation—2	4	No recurrences
4. Wide infiltration of urethra	2	Total amputation—1 Biopsy only—1 (refused further surgery)	Nil	Not known
5. Involvement of glans alone (previously circumcised in childhood)	3	Diathermy excision—2 Biopsy only—1 (refused further surgery)	2	One recurred (further treatment refused)
6. Extragenital (perianal)	1	Wide excision	1	Recurred—repeat excision carried out. Further follow-up lost
Total operated	24			
Number followed up	17			
Known recurrences	5			

Number treated by each method is more than the total number as some patients received secondary treatment for recurrence.

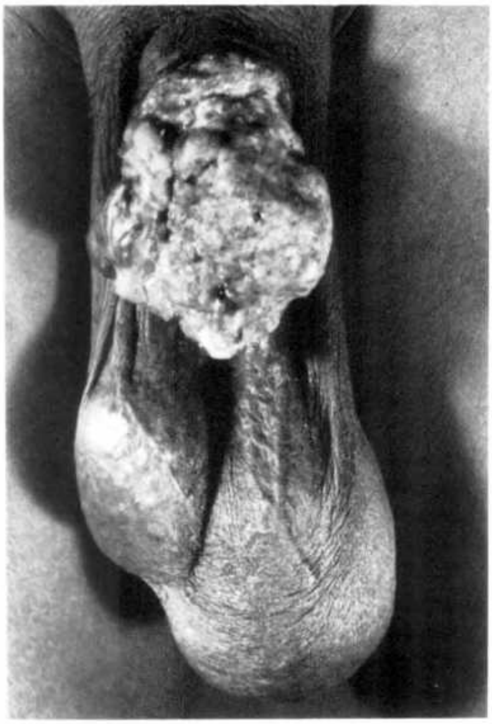

Fig. 2 Almost complete obstruction of the urethra by lesion of the glans.

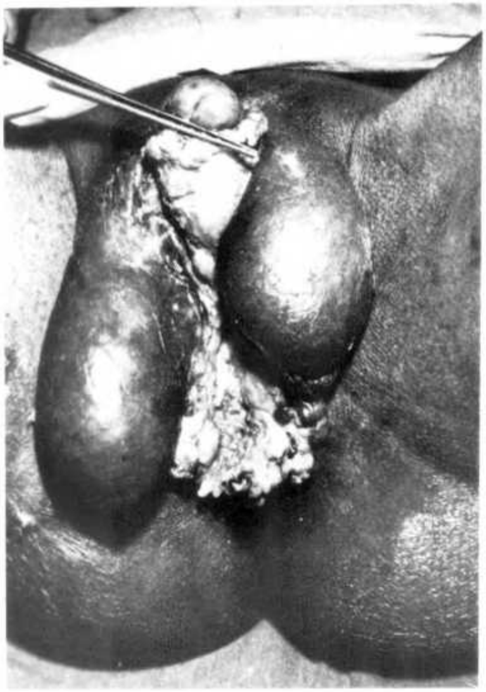

Fig. 3 Wide involvement of perineum, perianal region and penis in a case of Loewenstein-Buschke tumour of the penis.

Table 4 Pre-operative Clinical Diagnosis

Condyloma acuminatum	12
Granuloma venereum	1
Carcinoma of penis	8
Loewenstein-Buschke Tumour	3

operative biopsies and by histopathological examination of the excised specimen to exclude carcinoma. Treatment was surgical in all cases after lack of response to podophyllin in 11 cases.

Three early cases involving the prepuce and superficial portion of the glans were subjected to circumcision alone, with scraping away of the lesions on the glans with a knife (Table 3). Deeper penetrating lesions of the glans were excised with diathermy. Partial and total amputation of the penis was done on 3 occasions for extensive lesions. Two patients refused further surgical interference after preliminary biopsy.

Follow-up studies were possible in only 17 patients, 5 of whom showed recurrence 4 months to 7 years after initial surgery. Details of subsequent management are given in Table 3.

Discussion

A major difference between simple condylomata and invasive condylomatosis lies in the fact that no matter how large the ordinary condylomata, they are superficial and spare the underlying tissues (Dreyfuss and Neville, 1955; Dawson *et al.*, 1965), whereas the Loewenstein-Buschke

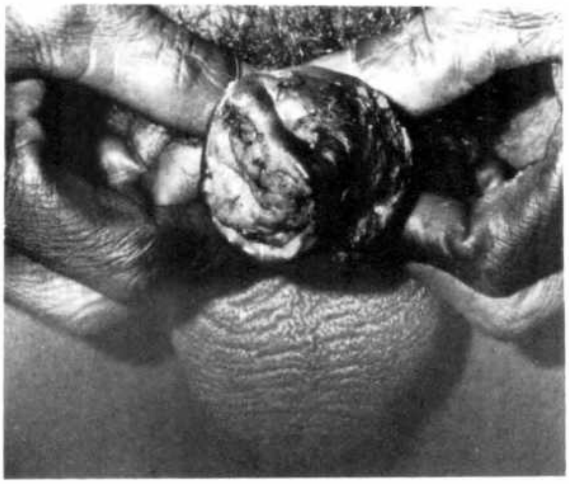

Fig. 4 Lesion clinically indistinguishable from an invasive carcinoma.

tumours have a pronounced tendency to downward growth, simulating malignant invasion. Histologically this growth in depth beneath the basement membrane is seen to be a mechanical displacement of normal tissues rather than the infiltration of tissues seen in malignancy (McCarron and Carlton, 1970). The lesion, therefore, while clinically indistinguishable from malignancy is histologically benign.

Buschke and Loewenstein (1925) believed that the tumour was restricted to males but recent reports have described similar lesions in females (Machacek and Weakley, 1960). While predominantly a lesion of the prepuce, similar tumours may appear in the oral mucosa (Netto *et al.*, 1976), rectum (Knoblich and Failing, 1967), perianal region (Dawson *et al.*, 1965) and the groin (Machacek and Weakley, 1960).

Ordinary condylomata acuminata are autoinoculable and transmissible lesions due to a filterable virus which appears identical with or related to the virus causing verruca vulgaris (Goldschmidt and Kligman, 1958). The precise aetiological agent for invasive condylomatosis remains obscure. However, histological similarity to condyloma acuminatum has been taken as presumptive evidence of a viral aetiology (McCarron and Carlton, 1970). The rapid invasive character of the lesions has been attributed to increased virulence of a viral agent or unknown factors affecting individual susceptibility (Netto *et al.*, 1976). Viral cultures were tried on He La cells in some of our patients without success.

Most of the reported patients have been uncircumcised males, as were 20 of our patients (Machacek and Weakley, 1960; Dawson *et al.*, 1965; McCarron and Carlton, 1970; Hudson *et al.*, 1973). It is felt that restriction of outward growth by a closely adherent preputial sac is the factor which predisposes to burrowing of deeper tissues, mimicking infiltration (Knoblich and Failing, 1967).

The natural history of the lesions is characteristically consistent. Commencing as a warty growth on or around the prepuce, the lesion gradually becomes nodular and penetrates underlying tissues, sometimes leading to the formation of sinus tracts (Dreyfuss and Neville, 1955; Dawson *et al.*, 1965). A putrid odour is prominent McCarron and Carlton, 1970; Netto *et al.*, 1976). The prepuce, glans and sometimes the shaft of the penis become completely destroyed by vegetative masses of tumour tissue. Regional lymph node enlargement due to secondary infection is often seen.

The true pathological significance of the lesion is still disputed, although it is generally held that the lesion, while clinically malignant, is histologically benign (Davis, 1965; Dawson *et al.*, 1965; Netto *et al.*, 1976). A few authors consider it to be a low grade squamous cell carcinoma (Machacek and Weakley, 1960; McCarron and Carlton, 1970). Dawson *et al.* (1965) claim to have demonstrated areas of transformation to malignancy. However, it is widely believed that though exhibiting a pronounced tendency to recur after local excision, transformation to an invasive squamous cell carcinoma is exceedingly rare (Machacek and Weakley, 1960). Histologically proved metastasis to the regional nodes or elsewhere has never been demonstrated.

Histological examination reveals an appearance closely resembling that of an ordinary condyloma (Figs. 5, 6). There is regularity of cell structure, marked acanthosis, infrequent mitosis and absence of invasion of blood vessel and nerves (Machacek and Weakley, 1960). Lymphocytic plasma cell and eosinophilic infiltration is prominent (Netto *et al.*, 1976). Epithelial downgrowths from tumour penetrating and compressing the underlying tissues are always seen. Basal layers may be multistratified, showing infrequent mitosis (Netto *et al.*, 1976). The basement mem-

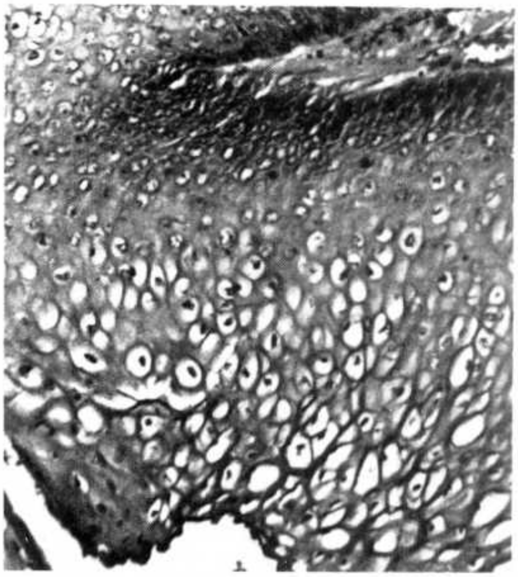

Fig. 5 Marked papillomatosis with vacuolation of epithelial cells (H and E × 166).

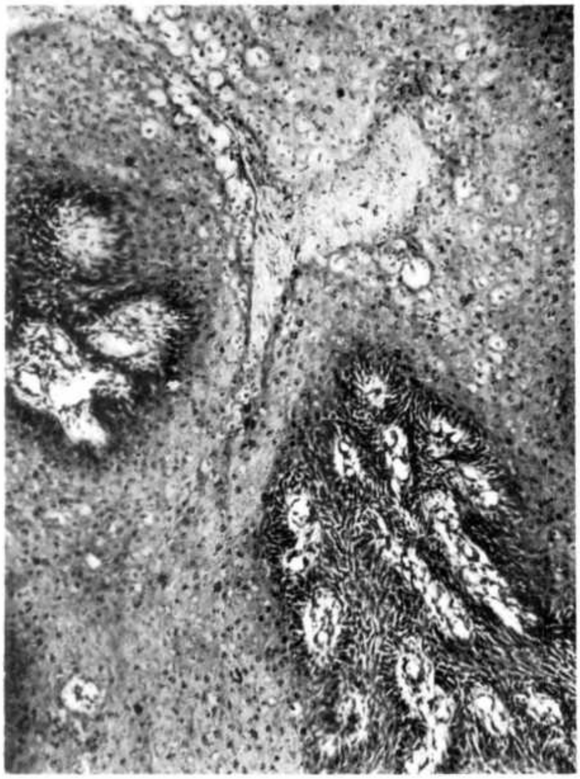

Fig. 6 Considerable acanthosis of the squamous epithelium resembling an invasive carcinoma. Scattered cells contain large hyperchromatic nuclei (H and E × 100).

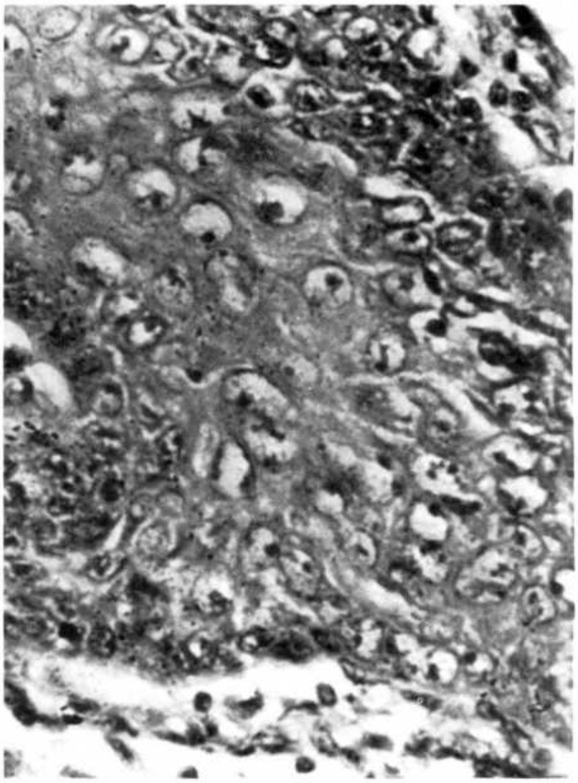

Fig. 7 Higher magnification of the acanthotic epithelium showing a benign appearance with intact basement membrane (H and E ×665).

brane is intact, though distorted (Knoblich and Failing, 1967). The lesions can easily be differentiated from carcinoma by the intactness of the basement membrane, preservation of cell polarity, absence of true infiltration of deeper structures as opposed to compression and displacement and absence of metastases (Fig. 7).

The importance of differentiating the Loewenstein-Buschke tumour from a true condyloma acuminatum lies in the fact that the former never responds to treatment with podophyllin, a procedure which may even lead to swelling of the epithelial cells and development of abnormal cells with a strong resemblance to malignancy, thus adding to confusion and hindering further treatment (Sullivan and King, 1947, 1948). In contrast to ordinary genital warts, the Loewenstein-Buschke lesions exhibit a greater degree of papillomatosis and acanthosis and a more prominent elongation of rete ridges. There is more active mitotic activity, individual cell keratinisation and keratin pearls (Knoblich and Failing, 1967). The increased tendency to grow deeply has already been mentioned (Machacek and Weakley, 1960).

Surgery is the treatment of choice and depending on the extent of the lesion and the degree of destruction of adjacent normal tissues, may vary from electrodesiccation to partial or even complete amputation of the penis. Incomplete excision leads to a tendency to local recurrence. Distant metastasis is practically unknown. Radiotherapy has been tried with very poor results (McCarron and Carlton, 1970; Hudson *et al.*, 1973; Netto *et al.*, 1976).

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A Low Power Magnification Technique for Reanastomosis of the Vas

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Summary—Microsurgical reanastomosis of the vas following vasectomy should result in a pregnancy rate of 65% and the reappearance of sperms within the semen of 95% of patients, but the technique requires expensive and sophisticated equipment and considerable expertise.

Comparable results were obtained using a simple and conventional technique in which fine sutures, splintage and low power magnification (× 3.5) were used, making it an acceptable procedure for the surgeon untrained in microsurgical techniques.

Remarkable successes have been achieved in recent years in the reanastomosis of the divided vas using microsurgical techniques (Owen, 1977; Silber, 1977). Such techniques require expensive equipment and an expertise acquired only after special training. This report shows that equally good results can be obtained using a meticulous but simple technique under low power magnification. Such a technique is well within the capacity of any competent surgeon.

Patients and Methods

Fifty patients, aged between 26 and 56 years and in whom a bilateral vasectomy for contraceptive purposes had been carried out from 14 months to 7 years previously, have undergone vasovasostomy.

The technique of end-to-end anastomosis of the divided vasa over a nylon splint, using fine interrupted silk sutures, was used in the majority of patients. In the first 5 patients a side-to-side technique as described by Mehta and Ramani (1970) was used but later abandoned as an end-to-end anastomosis seemed simpler.

In the end-to-end technique, each vas is approached through a small vertical scrotal incision, usually at the site of the previous vasectomy. The point of section of the vas is readily identified. It may be represented by a short slender segment of fibrosis or, on occasions, the vas is rejoined and the junction consists of vas of normal calibre with an obliterated lumen. Occasionally one or other of the divided ends is expanded like drumsticks and they may be joined together or, less frequently, widely separated. In all cases the divided ends should be identified and cut back until a normal lumen can be identified by passing a blunt-ended No. 22 hypodermic needle down both the proximal and distal ends. Usually the lumen of the proximal end is of greater calibre and frequently a milky fluid will ooze out. Each end should be mobilised to allow apposition without tension but the risk of interference with the blood supply that may occur with excessive mobilisation should be borne in mind. When the vas has been divided too far proximally, the proximal end is convoluted and cannulation difficult; careful dissection allows straightening of this part of the vas and subsequent cannulation.

A blunt-ended No. 22 hypodermic needle is then passed down the proximal vas and brought out through the wall of the vas about 2 to 3 cm from its end (Fig. 1). Alternatively, a blunt, atraumatic needle with nylon thread may be passed down the vas and brought out through its wall in the same way. A 30-cm length of 3/0 nylon is threaded

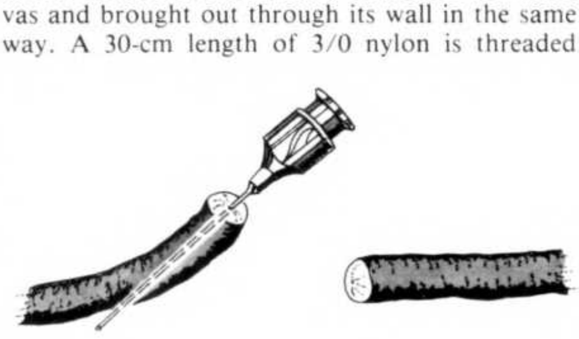

Fig. 1

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through the cannula and the cannula withdrawn over the nylon suture, leaving the nylon emerging from the lumen at the proximal end (Fig. 2). This end of nylon is threaded up the distal vas for some 20 to 25 cm (Fig. 3). The 2 ends of the vas are accurately opposed with 4 interrupted sutures of 7/0 silk (Fig. 4). The sutures pass through the muscle of the vas only and accuracy in placing these sutures is obtained by the use of magnifying spectacles (×3.5). It is important to obtain accurate apposition of these ends and, on occasions, more than 4 sutures may be necessary.

The free end of the nylon emerging from the proximal vas is led out through the adjacent scrotal skin and anchored with an Emesay button (Fig. 5). Two small holes bored peripherally on opposite sides of the button allow it to be anchored to the scrotal skin with nylon sutures (Fig. 6).

A scrotal support is used and the patient confined to bed for 48 h. Activity is limited for the first 2 to 3 days and gradually increased thereafter. The nylon splints are removed 6 to 8 days after the operation. Prophylactic Penbritin has usually been given for 7 days.

Results

Fifty patients have been operated on and in 42 patients motile sperms have reappeared in the ejaculate within one to 3 months following the procedure. In 26 patients (52%) their wives have had a normal pregnancy with the birth of a healthy child. One wife who became pregnant 3 months after the operation aborted spontaneously at 10 weeks and is not claimed as a pregnancy.

Discussion

There have been many reports published of series in which a conventional technique of end-to-end anastomosis of the vas over a nylon splint using fine sutures has been used (Table). The results vary but among the best reported are those of Phadke and Phadke (1967), with a 55% rate of pregnancy and an 83% incidence of sperms in the ejaculate. They used a simple nylon splint with three 6/0 arterial silk stitches passed through the seromuscular layer only. Fitzpatrick (1978), using a flap technique with a transverse anastomosis, achieved a pregnancy rate of 64% and the reappearance of sperms within the semen in 100% of 14 patients. Jenkins and Blacklock (1979), using four 3/0 Dexon sutures over a nylon splint, recorded 11 pregnancies (64.7%) in 17 patients.

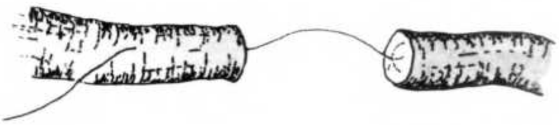

Fig. 3

On the other hand, the microsurgical technique as practised by Owen (1977) requires a 3-layer anastomosis carried out under an operating microscope capable of ×40 magnification. The mucosa is repaired with about six 10/0 Perlon sutures, the muscular layer with about twelve 8/0 nylon sutures, and the adventitia with a few 6/0 nylon sutures. In a series of 50 patients in whom sperms were identified in the proximal vas before proceeding, 98% showed sperms in their ejaculate 3 months after operation, and the pregnancy rate was 62%. Silber (1977), using a similar but 2-layered technique in 22 patients, obtained sperms in the ejaculate of 90% of these patients and a pregnancy rate of 50%.

By comparison, the author (Urquhart-Hay, 1980), using a conventional technique combined with oral prednisone 40 mg daily for a period of 6 weeks, obtained a pregnancy rate of 55% and a sperm rate of 95% in 20 patients.

Protagonists of microsurgical techniques emphasise that the conventional technique is a crude procedure which frequently creates a strictured, partially obstructed channel, or even a fistula.

Fernandes *et al.* (1968) claimed that splinting diminished anastomotic patency by causing

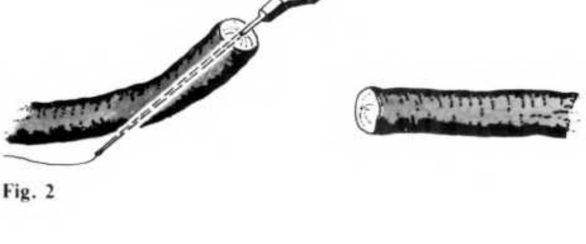

Fig. 2

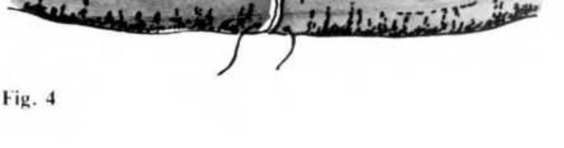

Fig. 4

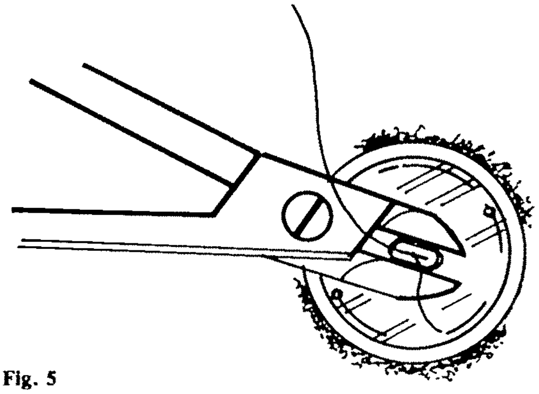

Fig. 5

mucosal damage with sperm leakage and eventual stricture formation. They claimed also that if the splint was left in place throughout the anastomosis and brought out through the walls of the vas, leakage and granuloma formation occurred even before the splint was removed.

The microsurgical technique may be a 1-, 2- or 3-layer anastomosis, but unexpected difficulties may be encountered in all. Belker *et al.* (1978) emphasised that considerable practice in the microsurgical laboratory is mandatory before actual performance of the procedure.

It is well known that there is a marked disparity between the number of patients in whom sperms return to the semen (which might be termed a technical success) and those who achieve a normal pregnancy (functional success). In the past this has been ascribed to an autoimmune response to sperms, due to the vasectomy, resulting in the appearance of sperm immobilising and sperm agglutinating antibodies in the serum. However, most now accept that this discrepancy is due to a continuing partial obstruction or, in those that fail completely, fibrotic obliteration of the anastomotic site. Since this difference between technical and functional success exists in all of the series published by microsurgeons, it suggests that microsurgical anastomoses also are not immune from the fibrosis of conventional methods.

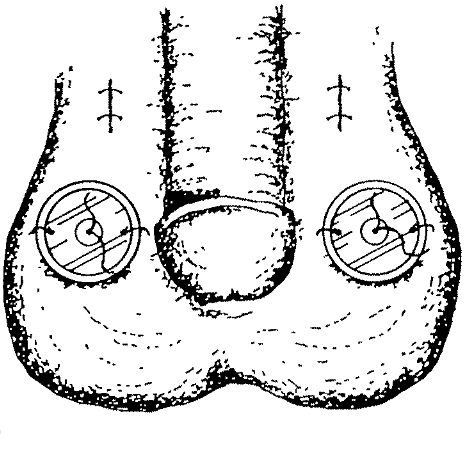

Fig. 6

Table

Author	*Number of patients*	*Sperms in ejaculate (%)*	*Pregnancy (%)*
Phadke and Phadke (1967)	76	83	55
Fitzpatrick (1978)	14	100	64
Jenkins and Blacklock (1979)	13	—	64.7
Urquhart-Hay (1980)	20	95	55
Owen (1977	50	98	62
Silber (1977)	22	90	50
Present Series	50	84	52

This present experience suggests that comparable results can be obtained using a conventional technique with low powered magnification (×3.5), meticulous placement of four 7/0 silk sutures in the muscle layer only over a fine nylon splint removed within 6 to 8 days.

The following points are emphasised in using this simple technique:

1. Minimal mobilisation of each vas end with as little disturbance as possible to its blood supply.
2. The smallest splint possible removed within 6 to 8 days.
3. Accurate apposition of the ends of the vas, using very accurately placed sutures to ensure a sperm-proof junction.
4. Forty-eight hours' bed-rest to prevent movement of the vas.
5. Resumption of coitus after 10 to 14 days to achieve a pregnancy as soon as possible.
6. Oral prednisone, 40 mg daily, for a period of 6 weeks may be of help in reducing fibrosis at the anastomotic site (Urquhart-Hay, 1980).

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The Effect of pH on the Urinary Inhibition of Calcium Oxalate Crystal Growth

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Summary—Urinary inhibition of calcium oxalate crystal growth was measured in metastable solutions of sodium oxalate and calcium chloride at different pH.

Inhibition of calcium oxalate crystal growth in urine from patients with calcium oxalate stone disease increased with increasing pH. The increase was most pronounced between pH 5.5 and 7.0

Sodium pyrophosphate in a similar way inhibited calcium oxalate crystal growth in this pH interval, and between pH 6.0 and 7.5 there was also a slight increase in the inhibiting activity by chondroitin sulphate and citrate.

Approximative correction factors were calculated in order to obtain a more appropriate value of the inhibition index when urine pH was different from 6.0, and a reasonably good correlation was obtained between inhibition indices calculated by means of the correction factor and inhibition indices derived from direct measurements of the crystal growth rate in solutions with different pH.

Crystallisation of calcium oxalate occurs in urine which is supersaturated with respect to this salt, and by aggregation of crystallites urinary concrements are subsequently formed. The processes of nucleation, crystal growth and aggregation of crystals are modified by urinary inhibitors of crystallisation. Several substances have been suggested as contributors to the total inhibition of calcium oxalate crystallisation, *i.e.* magnesium (Meyer and Smith, 1975; Backman *et al.*, 1979), citrate (Meyer and Smith, 1975; Baumann and Wacher, 1979) pyrophosphate (Fleisch and Bisaz, 1964; Baumann and Wacher, 1979; Sutor *et al.*, 1979) and macromolecular substances, probably acid mucopolysaccharides (Robertson *et al.*, 1978). The relative importance of these substances for the inhibition of calcium oxalate crystal growth in urine has not been completely evaluated.

Most authors, in their efforts to elucidate the effect of urinary inhibitors, have analysed the inhibitory activity *in vitro* in different crystallisation systems with constant ion strength and pH (Robertson *et al.*, 1973; Nancollas and Gardner, 1974; Will *et al.*, 1976).

It is known that the formation of calcium phosphate crystals is highly dependent on the urinary pH (Robertson, 1976), whereas the formation of calcium oxalate in a solution seems to be independent of variations in pH within the physiological range. On the contrary, very little information is available on the effect of pH on the activity of calcium oxalate crystal growth inhibitors, and the aim of the present study was to determine, *in vitro*, if the total inhibition of calcium oxalate crystal growth in diluted urine samples was affected by variations in pH.

Materials and Methods

Inhibition of calcium oxalate crystal growth was analysed following the addition of a small volume of urine to a seeded metastable solution of calcium chloride and sodium oxalate, with a composition mainly as described by Robertson *et al.* (1973).

The crystallisation solution contained calcium chloride (1 mmol/l), sodium oxalate (0.2 mmol/l) and sodium chloride (0.15 mol/l). The pH varied from 4.0 to 8.0 with a 10 mmol/l sodium cacodylate buffer. A tracer dose of ^{14}C-oxalate was added to the system (Tiselius, 1980).

The urine sample to be analysed was pre-heated to 37°C, carefully mixed and diluted to contain 5 μmol creatinine/ml. The urine was then filtered through a Millipore filter (0.22 μm) and 1 ml was

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subsequently added to the metastable solution, giving a final urine concentration around 1%.

Crystal growth was started by the addition of 2 ml of a suspension of calcium oxalate crystals (1 mg/ml) and the rate of crystallisation recorded by measuring the loss of ^{14}C-oxalate remaining in solution at different times during the first 2 h.

A control system containing 1 ml saline instead of urine was run in parallel with the urine solution at each pH.

Rate constants for the decrease in isotope in the system containing urine (k_u) and in the system containing saline (k_c) were determined and the inhibition index (I) calculated as described by Will *et al.* (1976):

$$I = 1 - \frac{k_u}{k_c}$$

One millilitre of solutions of chondroitin sulphate (0.75 mg/l, 5 mg/l and 10 mg/l), sodium pyrophosphate (30 μmol/l) and sodium citrate (1 mmol/l, pH 7) were similarly added to the crystallisation system and the inhibition index analysed at different pH.

Analyses were performed at pH 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5 and 8.0.

Based on the results in 13 different urine samples from patients with calcium oxalate stone disease, approximative correction factors were derived and a comparison performed between direct determination of the inhibition index at the current pH and a calculated value obtained by means of a correction factor.

Results

The mean inhibition index from 13 different urine samples in the pH interval 4.0 to 8.0 is shown in Figure 1. An increase in inhibiting activity was observed with increasing pH of the solution. The most pronounced rise was recorded between pH 5.5 and 7.0, with an increase in inhibition index from 0.56 to 0.69.

Figure 2 demonstrates the inhibition of crystal growth brought about by standard solutions of chondroitin sulphate (0.75 mg/l to 10 mg/l), giving final concentrations in the crystallisation system of 14, 93 and 187 μg/l. The inhibition at all concentrations was fairly constant up to 6.0, after which a slight increase was observed, most pronounced between pH 7.0 and 7.5.

Figure 3 shows the inhibition by a 30 μmol/l sodium pyrophosphate solution with a final con-

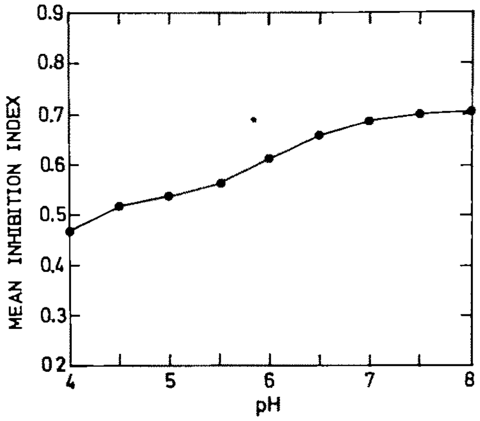

Fig. 1 Mean inhibition index at different pH of 13 urine samples from patients with urolithiasis.

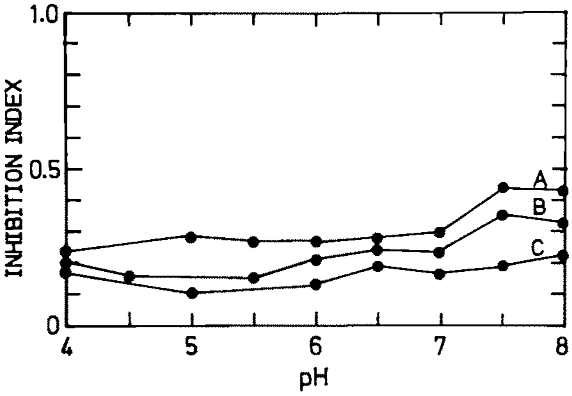

Fig. 2 The inhibiting activity on calcium oxalate crystal growth at different pH, brought about by chondroitin sulphate with concentrations in the crystallisation system of 187 μg/l (A), 93 μg/l (B), and 14 μg/l (C).

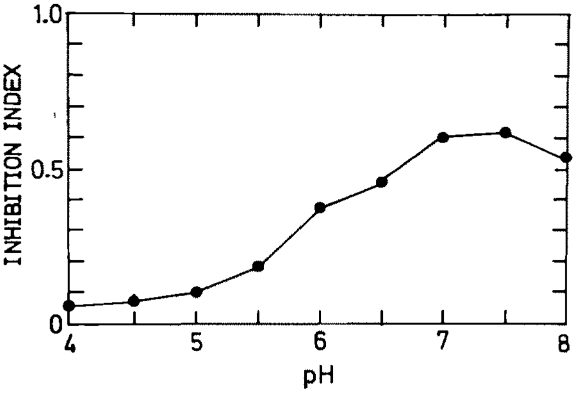

Fig. 3 The inhibiting activity on calcium oxalate crystal growth at different pH, brought about by sodium pyrophosphate with a concentration in the crystallisation system of 0.56 μmol/l.

centration in the system of 0.56 μmol/l. An increased inhibition between pH 5.0 and 7.0 was noted.

The inhibition of a citrate solution (1 mmol/l) with a final concentration in the system of 19 μmol/l is shown in Figure 4. A slight increase between pH 6.0 and 7.5 was found, with a rather constant inhibition index at lower pH values.

According to the results obtained from urine analysis, approximative correction factors were calculated. A factor 1.0 was given for the index obtained at pH 6.0, because our standard system for inhibition analysis was adjusted to pH 6.0 (Tiselius, 1980a). The correction factors are demonstrated graphically in Figure 5.

To check the validity of this correction the inhibition at different pH values was calculated from the index measured at pH 6.0 and compared with that obtained from direct determinations at each pH (Fig. 6). Although there is some scattering of the points in the diagram, the correlation is reasonably good and the correction factor appears valid for a rough estimation of the pH effect on the measured inhibition index.

Using those correction factors, an inhibition index of 0.50 at pH 6.0 would correspond to an index of 0.57 at a urine pH of 7.5 and 0.42 at pH 4.5.

Discussion

There is no simple method available to assess the inhibition of crystal growth in urine and it is therefore necessary to draw conclusions from measurements of calcium oxalate crystal growth inhibition in diluted urine samples. The method used in this study was adapted from the method described by Robertson *et al.* (1973). By studying the inhibitors in a diluted state, it is possible to obtain information on their physicochemical effects, but it is difficult to transfer directly these findings to the situation in concentrated urine. However, it can be assumed that factors affecting the inhibitors in their diluted state will also affect them in indiluted urine. There might also be differences between findings *in vitro* and effects *in vivo*.

Within the physiological pH range, the inhibition index for calcium oxalate crystal growth was found to increase in the pH interval 5.5 to 7.5. The physicochemical basis for this has not been investigated, but the effect is probably a result of changes in the ionisation of the different molecules responsible for the inhibitory effect.

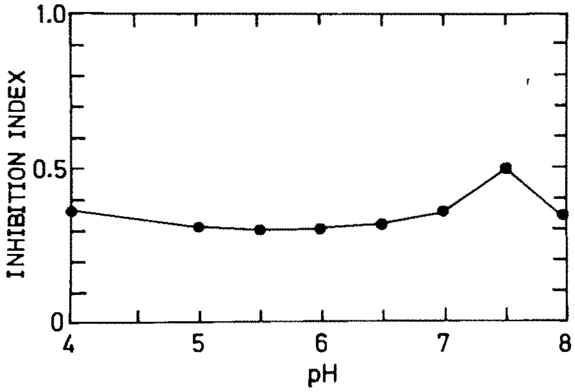

Fig. 4 The inhibiting activity on calcium oxalate crystal growth at different pH, brought about by citrate, with a concentration in the crystallisation system of 19 μmol/l.

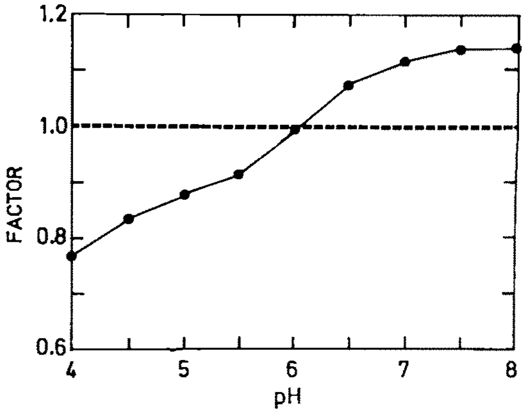

Fig. 5 Correction factors for calculation of the inhibition index at current urine pH, when this is different from 6.0.

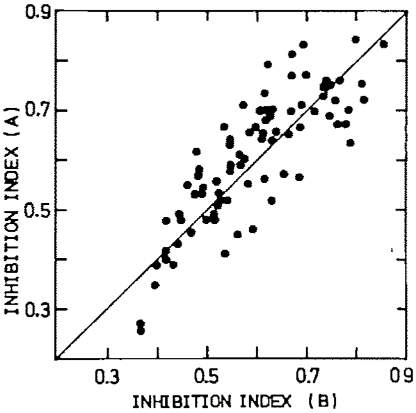

Fig. 6 Correlation between inhibition indices obtained from direct analysis at different pH values (A) and inhibition indices obtained from analysis at pH 6.0 and subsequently corrected by means of the correction factors in Figure 5.

The effect on inhibition of calcium phosphate crystal growth might be similar but has not been investigated and there is no information available in this respect. Since it is assumed that, in most stone forming patients, calcium oxalate crystal formation and growth is the primary step in stone formation (Hodgkinson, 1977), the effect of the inhibitors of calcium oxalate crystal growth is of fundamental importance. In order to find out which substance or substances in urine are responsible for the observed pH-dependent changes in inhibition, chondroitin sulphate, citrate and pyrophosphate were analysed with respect to their inhibitory activity. Chondroitin sulphate was used as an example of acid mucopolysaccharides, which have been suggested as potent inhibitors (Robertson *et al.*, 1978), but the exact nature of the inhibitory mucopolysaccharides in urine has not been established. Citrate was included because a significant effect of citrate on the inhibition of crystal growth was noted in a previous study (Tiselius, 1981). Pyrophosphate is also known to be a potent inhibitor both for calcium oxalate crystal growth (Baumann and Wacher, 1979) and calcium phosphate crystal growth (Fleisch and Neuman, 1961).

Citrate and chondroitin sulphate revealed only a slight increase in inhibitory activity in the relevant pH interval, whereas a pronounced increase was found for sodium pyrophosphate, and it seems reasonable to assume that in most urine samples pyrophosphate is the main determinant for the pH-dependent increase in inhibition of calcium oxalate crystal growth. However, in the pH interval 6.5 to 7.5 there might be a significant contribution even from citrate and mucopolysaccharides.

In a previous study (Bijvoet *et al.*, 1976) the calcium oxalate inhibiting activity of pyrophosphate was shown to increase when pH was changed from 5.0 to 6.0, and this was confirmed in the experiment presented here.

In addition to mucopolysaccharides, citrate and pyrophosphate, other substances might also contribute to the total urinary inhibitory activity (Fleisch, 1978; Tiselius *et al.*, 1981).

The effect of urinary pH on inhibition is, of course, strongly dependent on the distribution of different urinary inhibitors in the individual urine sample, and the correction factors used should be taken with great care and considered as approximate values, because differences in urine composition might significantly affect these factors.

The tendency to a lower inhibiting activity at low pH (4.0-4.5) is probably without physiological significance because of the increased solubility of calcium oxalate and the reduced rate of crystallisation in this pH region. On the contrary, the raised inhibition at higher pH might be more important.

It is possible that some patients with calcium oxalate stone disease would benefit from moderate alkalising therapy in order to obtain a reduced rate of crystal growth. However, an alkaline pH will result in an increased risk of calcium phosphate formation, particularly in patients with hypercalciuria.

A group of stone formers recently described by Polypchuk *et al.* (1979) showed increased excretion of calcium, decreased citrate excretion and a low pH. Moderate supplements of alkali would result in greater inhibition of calcium oxalate crystal growth and increased excretion of citrate, and could be of value in the prevention of renal stone formation in such patients. In patients with hypercalciuria this therapy should be combined with calcium reducing measures in order to avoid calcium phosphate stone formation, a risk that must be considered. No such studies have been carried out.

From the results presented in this study it appears that inhibitory activity with regard to calcium oxalate crystal growth must be evaluated in relation to the pH of urine.

Acknowledgement

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Case Reports

Sertoli Cell Tumour: a Reappraisal of Management

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In the classification of testicular tumours, lesions of the non-germ cells of the testis, particularly of Sertoli cells, are incorporated as a subgroup of the sex cord/mesenchyme tumours. We report a case of a Sertoli cell tumour and discuss its treatment.

Case Report

A 73-year-old man was admitted in February 1976 with an 8-month history of left scrotal swelling. Physical examination revealed a mobile, non-tender mass in the left hemiscrotum. With the exception of the erythrocyte sedimentation rate, routine laboratory and hormonal tests were normal, as were chest and skeletal X-rays, excretion urography and lymphography. Because the alpha-fetoprotein level was at the upper level of normal, a fine needle biopsy was carried out but this did not define the type of lesion.

The patient underwent left radical orchiectomy and retroperitoneal lymphadenectomy and recovered uneventfully. He has been followed up every 6 months and appears to be cured. The specimen measured 7.3 × 5.8 × 5.1 cm and microscopically revealed cylindrical, tubular and solid formations lined by Sertoli cells, elongaged cords with membranes including Call-Exner-like bodies, and microcysts filled with mucinous material

Comment

The Sertoli cell tumour has such variable histological and clinical features that it is difficult to assess its characteristic features.

By the end of 1978 we had collected 107 cases which might well be included in the group of "sex cord/mesenchyme" tumours. They are mainly benign, but we found the overall incidence of malignancy to be 16%—higher than the 10% reported by Mostofi and Price (1973) but lower than the 22% reported by Symington and Cameron (1976).

The risk of malignancy seems higher than previously considered, and so deceptive are the features and behaviour of this lesion (Koppikar and Sirsat, 1973) that we believe simple orchiectomy is no longer adequate treatment and that it should be complemented by retroperitoneal lymphadenectomy.

An early radical operative procedure may be more effective than radiotherapy, whose advantages have not yet been assessed (Symington and Cameron, 1976).

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Post-gonococcal Prostatic Cyst: an Unusual Abdominal Mass

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Cysts involving the prostate are uncommon and often pose a diagnostic challenge because of indefinite symptoms. They should be considered when an atypical mass is palpated on rectal examination. This case is unusual in that the mass was palpable on abdominal examination.

Case Report

A man aged 37 with a past history of gonorrhoea presented with difficulty in passing urine for 48 h, preceded by a one-week history of frequency and suprapubic discomfort.

Abdominal examination revealed a tender mass, dull to percussion, which arose from the pelvis and extended to the umbilicus. On rectal examination a soft mass was felt related to the upper part of the prostate, which otherwise felt normal. Since these signs were indistinguishable from a full bladder, initially a gonococcal stricture with retention of urine was suspected. The patient was catheterised, the urethra was found to be normal and 300 ml of concentrated urine drained. The abdominal mass remained unchanged. A cystogram, via the catheter, showed the bladder to be displaced forwards, upwards and to the left. A needle was then placed suprapubically into the mass and 100 ml of brown fluid drained; 50 ml of Hypaque was introduced and showed a large cavity. An IVU was then performed and showed both kidneys to be present (Fig.).

At laparotomy a large retroperitoneal cystic mass lying in the curve of the sacrum, attached to the posterior urethra and prostate, was excised. He made an uneventful recovery with catheter drainage for 2 weeks post-operatively and is well after one year.

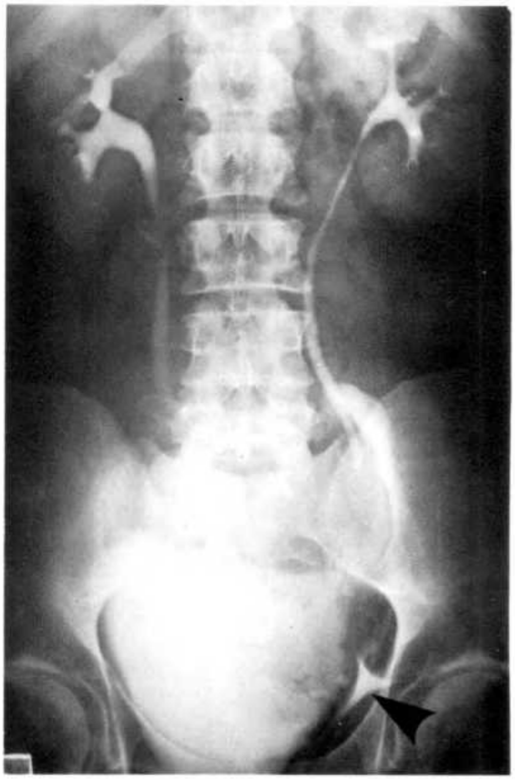

Fig. Intravenous urogram at 15 min following needling of cyst and injection of dye. The cyst is the large mass occupying most of the pelvis. The bladder, containing a catheter, is pushed over to the left (arrowed).

Comment

Rieser and Griffin (1964) described 4 types of cyst: Mullerian duct, seminal vesicle, ejaculatory and retention cysts of prostate. We have described a large midline cyst not containing sperm, thus consistent with origin from a Mullerian remnant. However, the cubical endometrial type of gland typical of the Mullerian duct cysts was not found, the cyst having a prostatic double layer. The histology is therefore supportive of an obstructive post-gonococcal aetiology. These cysts are associated with obstructive symptoms in 40% of cases and indirect evidence of urinary tract infection in 38% (Emmett and Witten, 1971).

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Ilioureteric Fistula

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Case Report

A 49-year-old male was referred to our clinic with gross haematuria. One year previously a left iliopopliteal bypass using a Gore-Tex prosthesis had been carried out for an occluded external iliac artery. The patient was still on anticoagulants. An intravenous urogram showed the left ureter to be dilated down to the pelvic vessels. At cystoscopy blood was identified from the left ureteric orifice. Arteriography (Fig.) revealed an anastomotic aneurysm of the obliterated prosthesis. After stopping anticoagulants haematuria ceased. At operation the ureter was scarred and there was a small fistula between it and the graft. Nephroureterectomy was performed and the bypass graft removed.

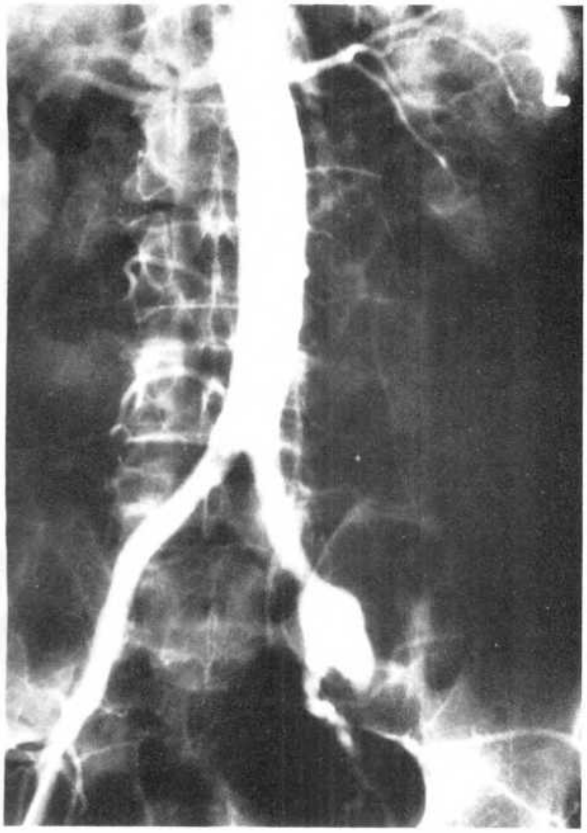

Fig.

Comment

Ureteric obstructions after reconstructive surgery with synthetic vessel grafts are quite frequent (Giessler *et al.*, 1969; Petrone *et al.*, 1974), and normally observed where the ureter crosses the iliac vessels when there is an aneurysm of the iliac artery at the anastomosis of a bypass graft or patch. Ureteric obstruction may also occur if an aortic femoral bypass is placed in front of and not behind the ureter.

Ilioureteric fistulas with gross haematuria are very rare. In this case the anastomotic aneurysm first obstructed the ureter and later eroded the ureteric wall, forming an ilioureteric fistula.

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A Case of Ureteric Obstruction due to a Double Right Vena Cava Forming a Periureteric Venous Ring

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Loin pain is a common presentation of ureteric obstruction, but vascular causes are rare and may not be considered. A case is described of a retrocaval ureter with a double right vena cava which had radiological features distinct from the usual type of retrocaval ureter.

Case Report

J.McL., aged 22, first presented with his fifth episode of right loin pain in 2 years. All investigations were normal except for an intravenous urogram (Fig. 1) which showed dilatation of the right ureter to the level of L3, below which it formed an inverted J shape and was deviated towards but not up to the midline. At operation the kidney was normal but the pelvis was dilated to where it passed through a periureteric venous ring. As illustrated in Figure 2, the ring was composed of a double right vena cava. The lateral segment of the double right vena cava along with the stenosed part of the ureter was resected and the ureter reconstructed. Follow-up IVU showed reduced dilatation.

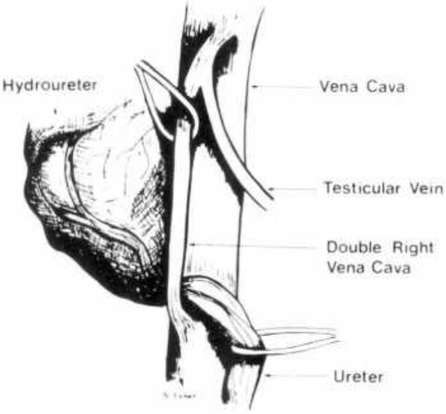

Fig. 2 Diagram of operative findings. Note that the lower ureter is retracted medially to show the obstruction by the venous ring.

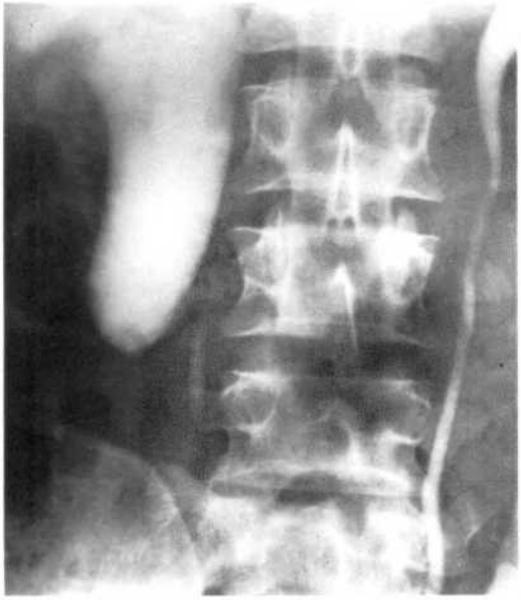

Fig. 1 Intravenous urogram showing hydroureter with reversed J shape ureter below the obstruction.

Comment

There have been 3 previous reports of a periureteric venous ring (LePage and Baldwin, 1972; Irikura *et al.*, 1973; Fujioka *et al.*, 1977) in which the lateral portion of the vena cava is short and the site of obstruction is at the lower junction of the 2 right venae cavae. Cases have been described in which there is no venous ring but the double cava arises in the pelvis. Such an abnormality may be explained embryologically by persistence of the posterior cardinal vein as the lateral limb of the double post-renal segment of the inferior vena cava. Deviation of the ureter to the midline below the reversed J shape is the radiological feature of a retrocaval ureter. However, in this case and in the others reported the deviation, although medial, is not up to the midline.

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Dermoid Cyst of the Prostate with Contralateral Renal Agenesis

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Case Report

A 50-year-old man was admitted to hospital with perineal discomfort and dysuria. The only abnormal finding on physical examination was a tender swelling which seemed to be connected with the left prostatic lobe. The intravenous urogram showed a large left kidney and a space occupying lesion in the left bladder wall. There was no functioning right kidney (Fig. 1). Renal arteriography revealed a solitary left kidney with a single renal artery. Vesiculography showed a prostatic urethra with 2 normal seminal vesicles displaced to the right (Fig. 2).

On urethrocystoscopy the colliculus seminalis seemed to be enlarged but the prostate was of normal size. The left bladder wall was elevated and impressed from the outside. There was no ureteric orifice on the right. Ultrasonography showed a pear-shaped cyst containing solid material. At operation a 10 × 6 × 6 cm cystic tumour was dissected from the left prostatic lobe. It contained thick brown paste and hair. The connection with the prostate resembled a cord and was not open. The post-operative course was uneventful and the patient was discharged with improved micturition. Histological examination showed a dermoid cyst with no other typical features.

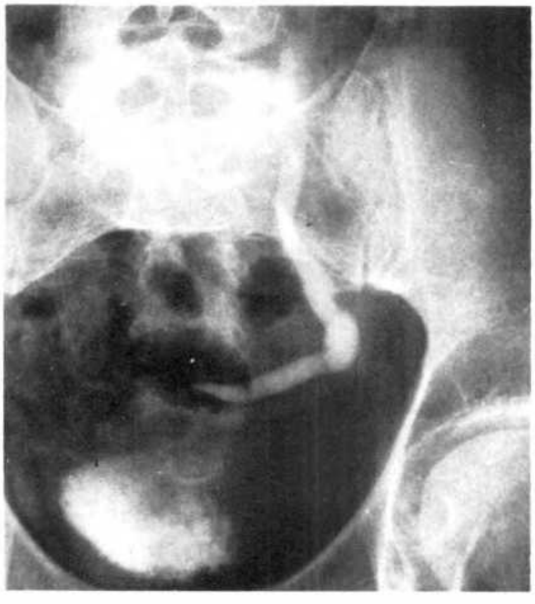

Fig. 1 Mildly dilated left ureter with atypical intrapelvic course. Incomplete filling of left bladder wall. No right kidney.

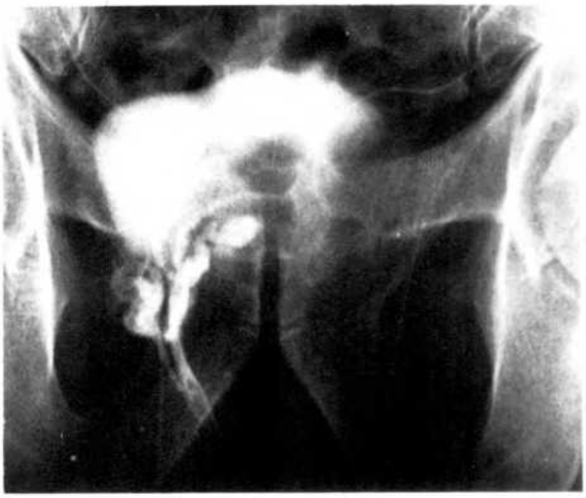

Fig. 2 Displacement of prostatic urethra and seminal vesicles to the right. Impression and elevation of left bladder wall.

Comment

There are several cystic tumours of the male pelvis which interfere with micturition (seminal vesicle, utriculus and Echinococcus cysts) but a dermoid cyst has, to our knowledge, not been described. Dermoid cysts have been reported in the testes and the scrotum (Champion, 1974; Gupta *et al.*, 1974) and in the rectovesical space (Wilson, 1973).

Dermoid cysts may be distinguished from other cysts by ultrasonography, which reveals their solid contents.

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Spontaneous Rupture of Solitary Functioning Kidney

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Case Report

A 58-year-old male had conservative treatment for proteinuria and microhaematuria for 2 days. He suddenly developed severe right loin pain with macrohaematuria. His blood pressure dropped and he was sent to our clinic as an emergency. Intravenous urography revealed severe hydronephrosis of the right kidney and non-function of the left kidney with capsular calcification. Selective arteriography (Fig.) showed that the right kidney had ruptured spontaneously and a nephrostomy was performed. Although his general condition improved, he died suddenly of ileus about 2 months after operation.

At autopsy it was revealed that, in addition to pelviureteric junction stenosis, the right ureter was occluded and infiltrated by malignant mesothelioma. The left kidney appeared like a large cyst with calcification, probably due to pelviureteric junction obstruction.

Comment

Spontaneous rupture of the kidney is a rare occurrence and seldom affects a solitary functioning kidney. There have been only 2 previous reports of such a case, the first by Jewell (1964) and the second by Main (1967). In the former case there was congenital absence of the contralateral kidney and, in the latter, the cause of non-function of the contralateral kidney was unknown. In this, the third reported case, the cause of non-function of the contralateral kidney was thought to be congenital pelviureteric junction obstruction.

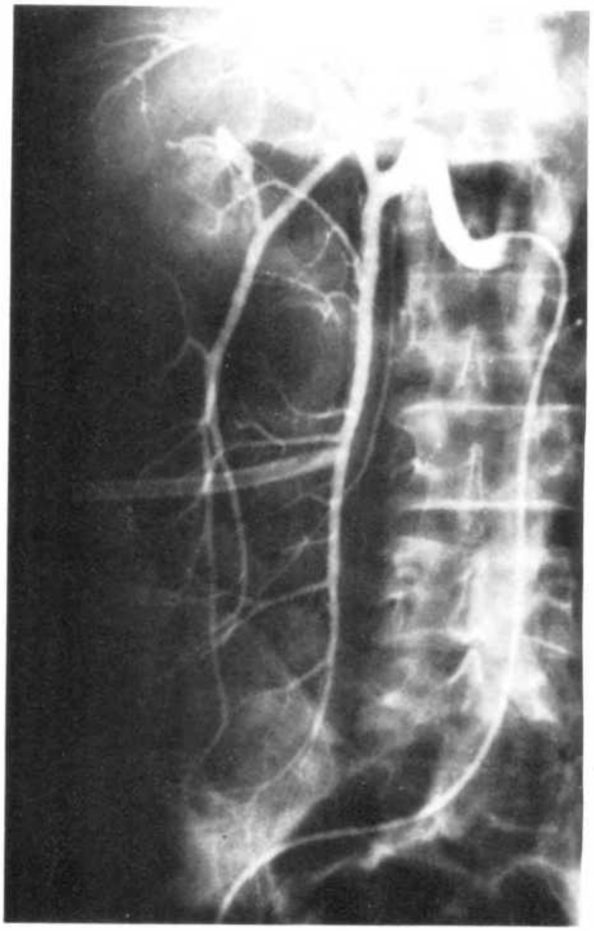

Fig. Right renal arteriogram: severe hydronephrosis is shown with active bleeding spot in the upper pole (arrow).

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Bilateral Renal Stones in a Haemophiliac

W. B. WATERFALL, *formerly Consultant Surgeon and Urologist, Plymouth General Hospital*

Major operations have become feasible in haemophilia since Factor VIII concentrates have been available. Large series have been described (Biggs, 1966; Kernoff, 1972; Aledort, 1975) but there has been no report of conservative renal surgery in a severe haemophiliac.

Case Report

C.V., a male aged 28 years, was a classical haemophiliac A, with no measurable Factor VIII. He had suffered from numerous haemarthroses and had had haematuria since childhood. In 1973 when Factor VIII inhibitors were noted, the haematuria became worse and renal stones were shown. In 1975 a urogram showed that these were causing back pressure, worse on the right. Serum electrolytes and calcium excretion were normal (Fig. 1).

The stones on the right were removed first and, 9 months later, those on the left were removed. On both occasions a reducing scale of intravenous infusions of Factor VIII was adjusted to give a minimum plasma concentration of 40% over 14 days. Despite adequate blood levels he bled heavily on the sixth day after each operation and he still had a residual haematoma on the left 6 months after the operation (Fig. 2). He has had several further haemarthroses but no more haematuria.

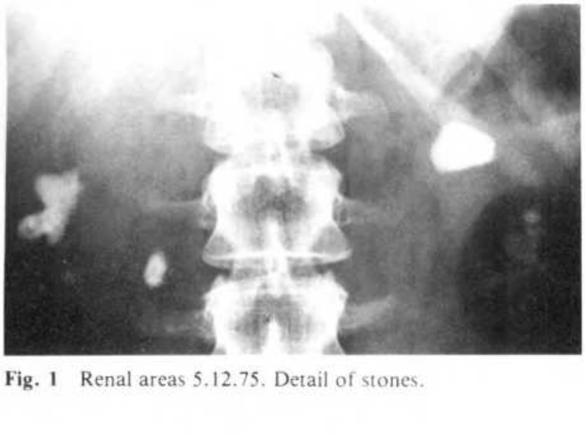

Fig. 1 Renal areas 5.12.75. Detail of stones.

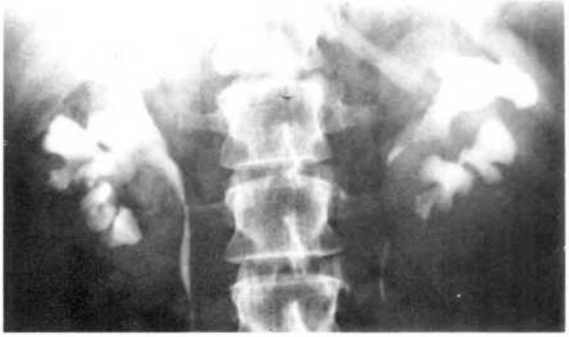

Fig. 2 Intravenous urogram (25-min film) 14.3.77. Shows good function and free drainage despite haematoma on the left.

Comment

Factor VIII infusions can give relatively normal operating conditions in haemophilia, but dangerous bleeding may occur when the dosage is reduced.

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Prostatism, Obstructive Uropathy and Uraemia Associated with a Urachal Cyst

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Lesions of the urachus are uncommon and usually present only when complications occur. This is a case of urinary retention and uraemia secondary to infection of a urachal cyst.

Case Report

A 54-year-old man was admitted with acute on chronic urinary retention following 4 days' treatment at home with co-trimoxazole. He was catheterised and 700 ml turbid urine obtained. Blood urea was 27.8 mmol/l and creatinine 441 μmol/l. A mid-stream specimen of urine contained white blood cells but was sterile on culture. All other investigations were normal. He was treated with noxythiolin 2.5% bladder wash-outs twice daily. Blood urea and creatinine rapidly returned to normal. Intravenous urography showed early obstructive changes in both kidneys and ureters (Fig.). Cystoscopy revealed an inflamed bladder with an area of polypoid, ulcerated mucosa in the midline superiorly. Examination under anaesthesia revealed a smooth, mobile mass above the bladder. Biopsy showed squamous metaplasia and inflammatory changes. A barium enema showed no intrinsic lesion. Laparatomy revealed an extraperitoneal mass attached to the dome of the bladder. The mass was excised with the dome of the bladder. Histological examination showed a fibrous wall lined with inflammatory granulation tissue. There was a narrow track connecting the bladder to the mass.

When reviewed 3 months after operation the patient was asymptomatic with a normal blood urea. IVU showed minimal upper tract dilatation and no residual urine.

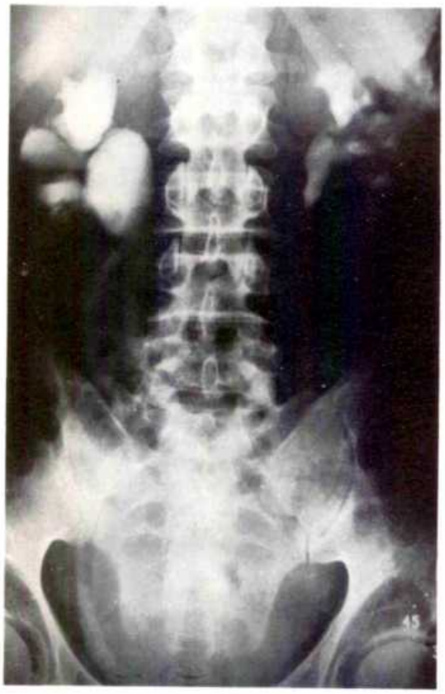

Fig.

Comment

The urachus develops from either the allantois (Cullen, 1916) or the cloaca (Begg, 1930). It extends upwards from the dome of the bladder and is attached to the obliterated umbilical arteries. If obliteration of the lumen is incomplete, one of 4 anomalies occurs:

(*a*) communication with the bladder,
(*b*) communication with the umbilicus,
(*c*) a patent fistula between bladder and umbilicus,
(*d*) a non-communicating cyst.

There are no reported cases of a urachal anomaly presenting with retention, though Breschi (1969) reported a case of prostatism associated with an infected urachal cyst.

We believe that in our patient infection in a urachal cyst led to secondary prostatic infection with consequent oedema and inflammatory reaction in the prostate, producing acute on chronic retention with mild obstructive renal changes. Complete functional and symptomatic relief was achieved by excision of the cyst and partial cystectomy without bladder neck or prostatic resection.

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Notices

British Association of Urological Surgeons

President: W. K. Yeates, MD, MS, FRCS

Annual Meeting: Newcastle upon Tyne, 7-9 July 1982.

Abstracts of papers to be considered by Council for this meeting should be submitted to the Honorary Secretary by 4 January 1982. An abstract must be typed on a single sheet of A4 paper and consist of no more than 200 words. UK contributors must submit 30 copies of their abstract: other contributors may send one copy only.

All correspondence to: J. Vinnicombe, MChir, FRCS, Honorary Secretary, British Association of Urological Surgeons, at the Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

Institute of Urology (University of London) in association with St Peter's Hospitals

Preliminary Announcement of Seminars to be held Autumn 1981 to Summer 1982.

Autumn Term
Iatrogenic problems in urology
Renal homeostasis
Ureteric replacement
Uro-radiology weekend
Review of the year in urology

Spring Term
Ten-week course "Urological Practice"
25 January to 2 April 1982
Paediatric urology
Renal intensive care

Summer Term
Recent advances in renal surgery
Sexual problems in urological practice
Endoscopic urology
Operative urology
Computer applications in urology

Applications to the Courses Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel. 01-836 5361 Ext. 30 or 01-836 2711 Ext. 30.

Medical Research Council

Proposed Clinical Trial

A multicentre trial of intravesical thiotepa in new cases of superficial bladder cancer has been planned. The trial will commence in the autumn of 1981 and the MRC Working Party on Bladder Cancer will welcome participation by interested urologists.

Further details from: Mr B. Richards, Department of Urology, York District Hospital, Wigginton Road, York YO3 7HF.

International Symposium on Renal Tumours

Paris, France. 9-11 November 1981.

Further information from: Professor S. Khoury, Clinique Urologique, Hôpital de la Pitié, 83, boulevard de l'Hôpital, 75634 Paris Cédex 13, France.

The Urological Society of Australasia. Annual Scientific Meeting, Canberra, Australia

28 March to 1 April 1982.

Further particulars from: J. Boulas, Suite 44, RPAH Medical Centre, 100 Carillon Avenue, Newtown, NSW 2042, Australia.

Athenian Days of Urology

Athens, Greece. 8 and 9 May 1982.

The main subject will be "What's New in Urology?"

Further particulars from: Professor C. Dimopoulos, University of Athens, Urological Department, King Paul's Hospital, Goudi, Athens, Greece.

Third Copenhagen Symposium on Transurethral Surgery

Copenhagen, Denmark. 11-14 January 1982.

Language: English. Live TV, lectures, panels.

Further particulars from: F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.

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Book Reviews

Human Artificial Insemination and Semen Preservation. Edited by G. David and W. S. Price. Pp. 639. New York: Plenum Press. 1980. Price US $65.00.

This comprehensive book, which deals with artificial insemination by donor and by husband, will form a useful source of reference in specialist centres where this type of treatment is undertaken. The section on artificial insemination by husband is of interest to urologists who have an infertility clinic, but provides no evidence to show that this form of treatment for cases of oligozoospermia improves on the pregnancy rate seen by chance. The case for artificial insemination by husband where antisperm antibodies have been detected is an interesting possibility but not yet proven. A useful reference book for specialist clinics.

Principles of Pathology in Surgery. K. A. Myers, R. D. Marshall and J. Freidin. Pp. xi + 453. Oxford: Blackwell Scientific Publications. 1980. Price £12.00.

The authors, all surgeons, aim at explaining "the problems of surgery in terms of pathological principles". The book is an applied text on general pathology for surgeons with chapters on focal lesions, infections, healing processes, tumours, haemorrhage, body fluid disorders, immunology, atherosclerosis and shock. It is profusely illustrated with very good line diagrams drawn by one of the authors, J. Freidin, and his drawings of microscopic sections are particularly impressive.

This is an excellent book for undergraduate and postgraduate surgical students.

The Year Book of Urology 1980. Edited by J. Y. Gillenwater and S. S. Howards. Pp. 366. Chicago, London: Year Book Medical Publishers. 1980. Price £24.00.

Your reviewer began his own collection of the *Year Book of Urology* in 1961/62. In the ensuing 20 years the size and style have changed very little but there has been a considerable sharpening of the comment that follows each of the review articles. Even in 1961 there were helpful editorial comments following many of the main features, but by 1980 this has become a very established format and those commenting upon each of the review articles must be rated as acknowledged experts on that particular topic. This year, under the editorship of Gillenwater and Howards, the format and standard are well maintained and the editorial comments remain a first-class feature of the book.

It is true that all urologists hope to have kept up with the literature and would not need to read a book such as this. However, the fact is that this book remains the best concise summary of the urological literature and is not only a "must" for any desert island urologist but also for many others, even those close to extensive libraries.

Atlas of Operative Andrology. A. Kelami. Pp. x + 202. Berlin: Walter de Gruyter. 1980. Price DM 174.00.

The title of this atlas could cause confusion, since it is an atlas of male urological surgery that excludes the kidney and ureter but includes the various forms of prostatectomy and reconstruction of the urethra. Thus, the urological surgeon who may wish to purchase this atlas to learn about such procedures as transurethral resection of the prostate might also wish for details of operations on the ureter and kidney. On the other hand, the andrologist who is concerned with operations such as epididymovasostomy or vasovasostomy might like details of alternative techniques available in difficult situations, *e.g.* vas reconstruction in a case where large segments of vas are missing. The operations that are covered are described well and the drawings are clear. The book may find a place alongside other standard operative surgery manuals when alternative techniques are being sought.

The Infertile Couple. Edited by R. J. Pepperell, B. Hudson and C. Wood. Pp 252. Edinburgh: Churchill Livingstone. 1980. Price £10.00.

This is a sensible book which outlines the current concepts of diagnosis and treatment of female and male infertility. It is surprising that the combined management of the infertile couple is seldom dealt with in a single volume. The chapters on cervical and immunological factors in infertility, unexplained infertility and artificial insemination are particularly recommended to the urologist who runs the male side of a urological/gynaecological infertility service, for they highlight areas that are not always well understood by the specialist who has concentrated on assessment of the male.

The book is small enough not to be daunting and is highly recommended to those with an interest in infertility, male or female.

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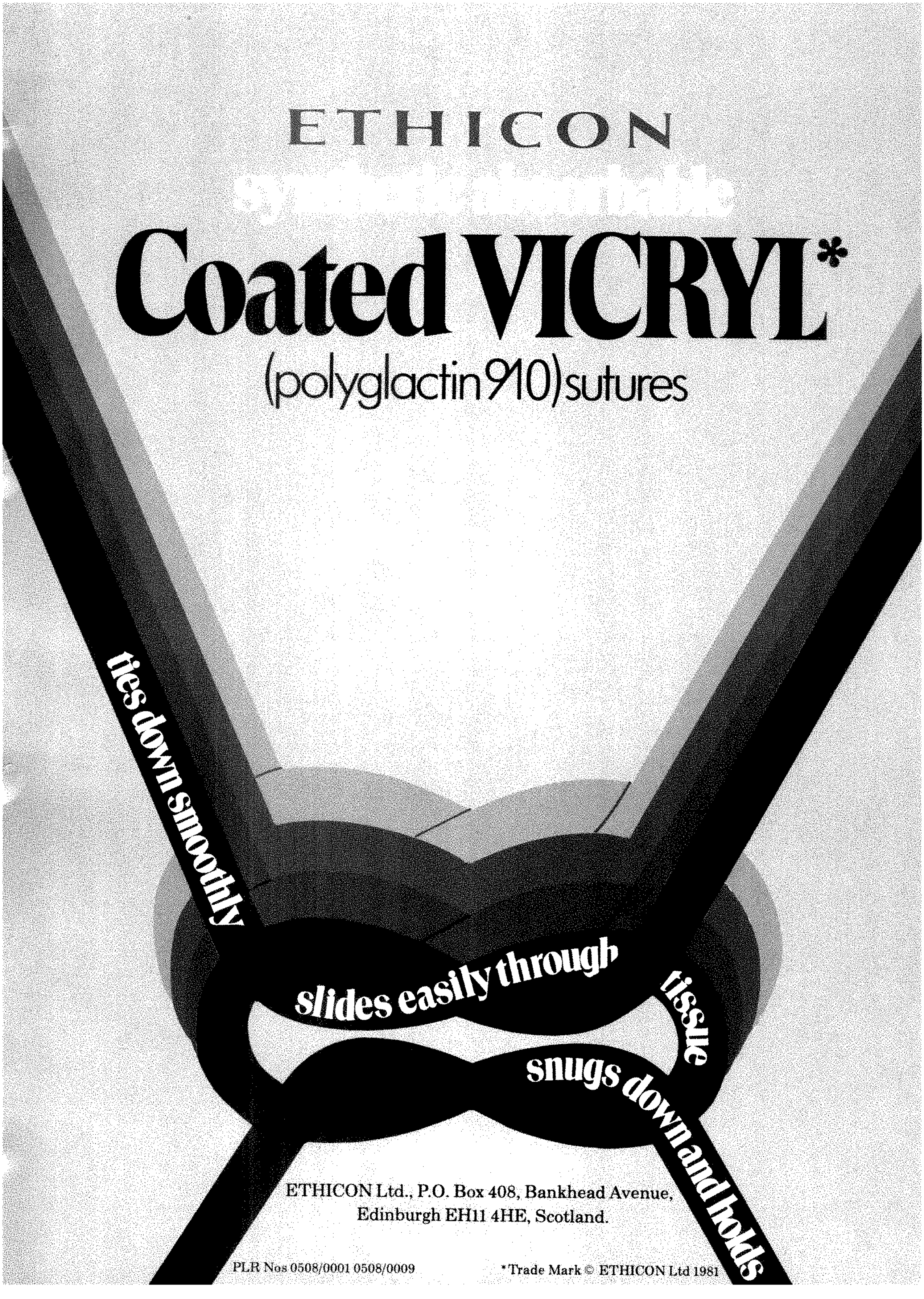

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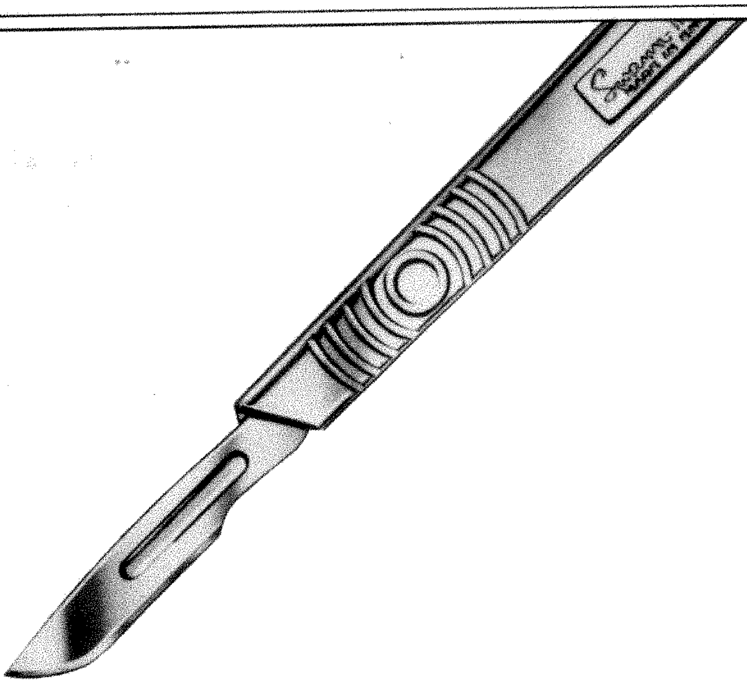

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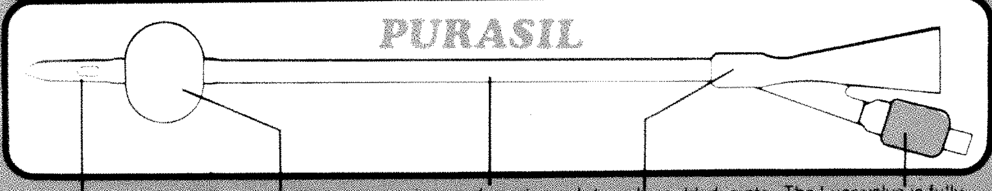

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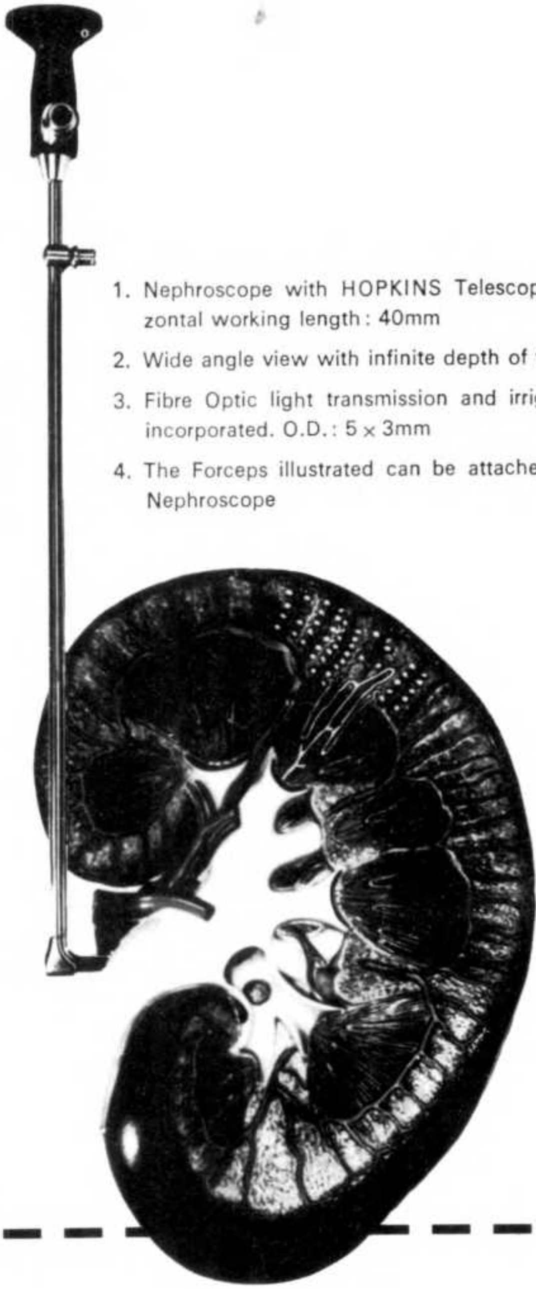

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Mogens Asmussen MD, DrMed, *formerly Clinical Research Fellow, Gynaecological Department, Norwegian Radium Hospital*
and Ashton Miller MA, MD, FRCS, *Emeritus Consultant Urologist, United Bristol Hospitals*

This text is unique in that all problems are considered from both the gynaecologist's and urologist's point of view, thus filling a gap which has come about as a result of increasing specialisation in training. It provides the trainee and gynaecologist in hospital and private practice with the necessary knowledge to recognise and treat urological problems, particularly emergencies with which he may be faced; urologists will find information about the many gynaecological conditions which may produce urinary symptoms, including gynaecological oncology.

December 1981. 224 pages, 198 illustrations.
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Contents

Introduction; Applied embryology, anatomy and physiology; Urinary symptomatology; Examination of the urinary tract; Urine examination; Urinary tract infections; The effect of pregnancy on the urinary tract; Classification of dysfunction of the lower urinary tract; Stress incontinence; Neuropathic dysfunction; Idiopathic dysfunction; The urinary tract at gynaecological laparotomy; Standard gynaecological operations: avoidance and management of injury to the urinary tract; Standard urological operations which the gynaecologist may need; Gynaecological cancer surgery and the urinary tract; The urinary tract and radiotherapy; Urinary fistula; Practical help for the woman with urinary incontinence; Benign and malignant conditions in the urethra.

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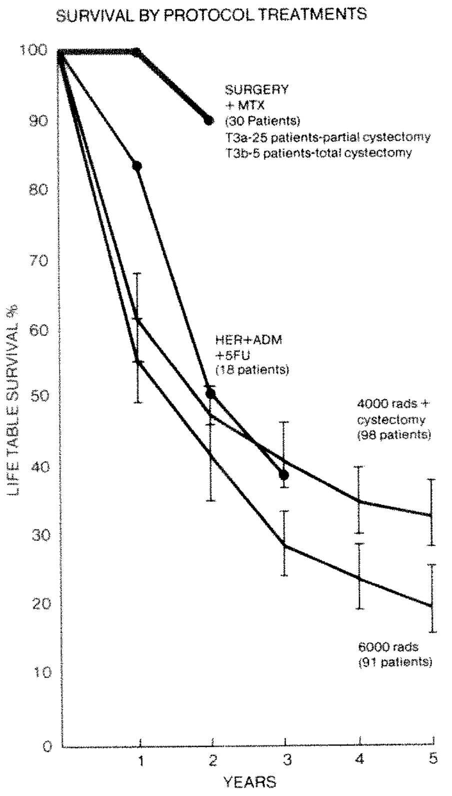

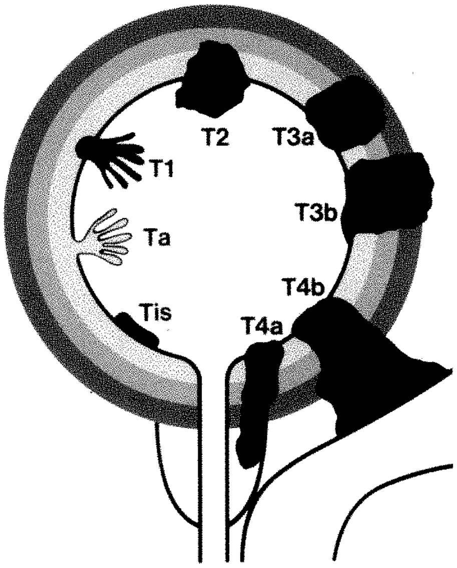

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1. Smith PH. Paper read at *International Symposium on Methotrexate*, London 1979. *Cancer Treatment Reports*. In Press.
2. Socquet Y. *Ibid.*
3. Calvert AH and Turnbull CP. *Cancer Treatment Reports*. In Press.

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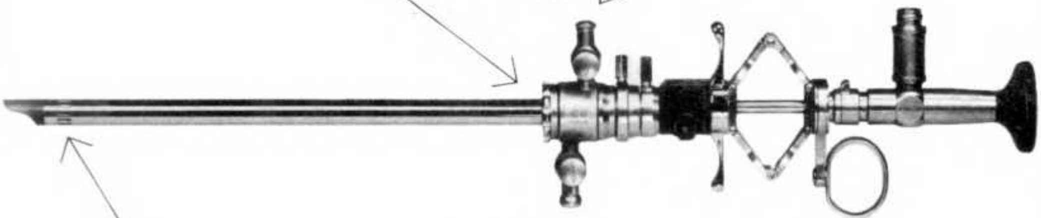

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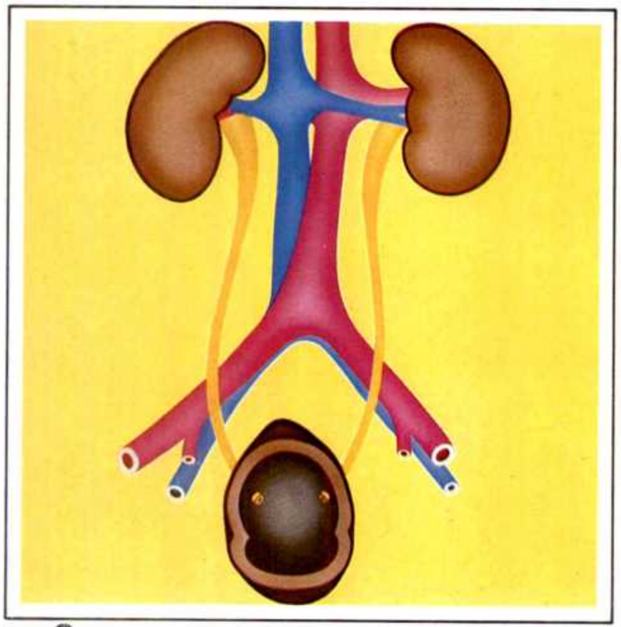

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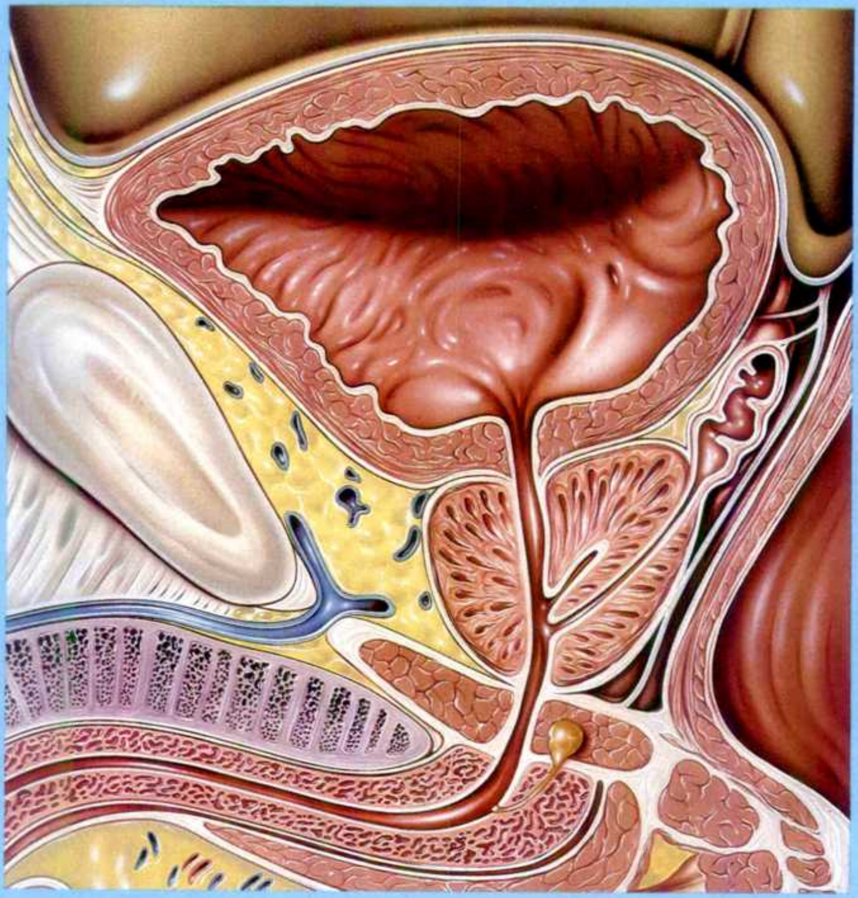

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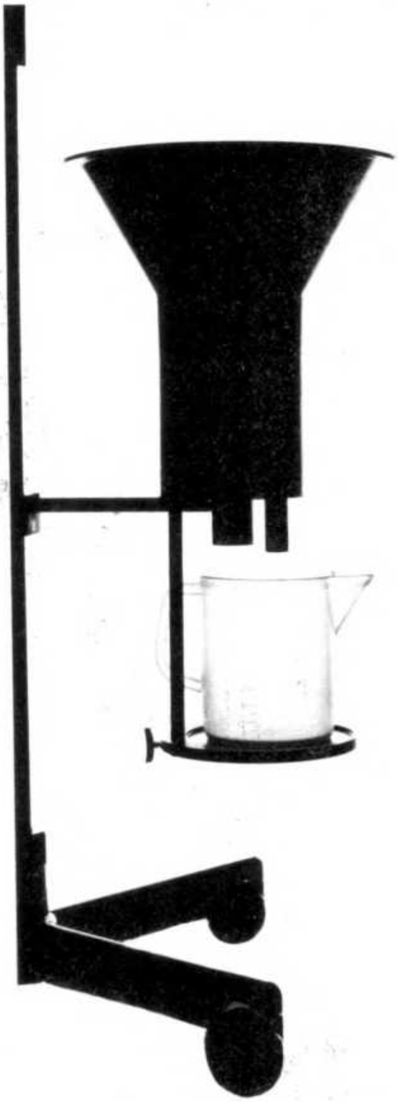

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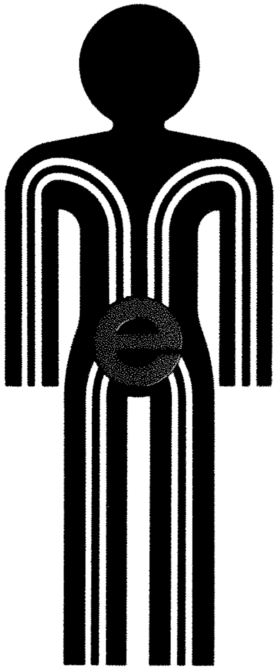

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1. Nagel, R. and Kolln, C-P.: Treatment of Advanced Carcinoma of the Prostate with Estramustine Phosphate (1977). Brit. J. Urol., 49, 73-79. 2. Mayer, E.J. Orale Estracyt-Behandlung beim Prostatakarzinoma (1975) Ther. Umschau, 32, 114-119. 3. Jonsson, G., Hogberg, B. and Nilsson, T.: Treatment of Advanced Prostatic Carcinoma with Estramustine Phosphate (Estracyt) (1977). Scand. J. Urol. Nephrol., 111: 231-238. 4. Mittleman, A., Shukla, S. K. and Murphy, G. P.: Extended Therapy of Stage D Carcinoma of the Prostate with Oral Estracyt (1976). J. Urol., 115, 409-412.

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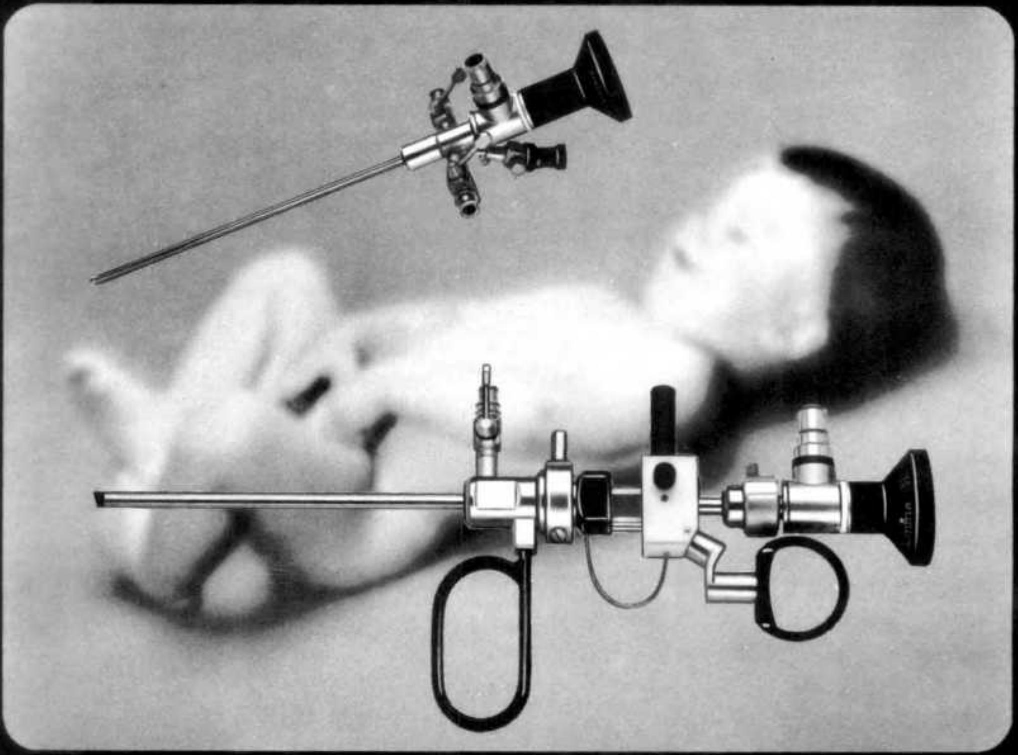

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The Influence of Renal Prostaglandins on Glomerular Filtration Rate (GFR) and Calcium Excretion in Urolithiasis

A. C. BUCK, W. F. SAMPSON, C. J. LOTE and N. J. BLACKLOCK

Department of Urology, Royal Naval Hospital, Haslar

Summary—In a clinical study of 275 idiopathic stone formers the GFR was significantly raised in hypercalciuric patients compared with normal controls $P < 0.001$). The possibility that the mechanism underlying hypercalciuria and raised GFR may be prostaglandin-mediated was considered because it is now well established that prostaglandins regulate intra-renal haemodynamics and influence tubular electrolyte excretion.

Experiments were performed in conscious Sprague Dawley rats to determine the changes in calcium and sodium excretion following prostaglandin synthetase inhibition with indomethacin. Both calcium and sodium excretion together with urine flow were significantly reduced ($P < 0.002$). Further experiments were performed in anaesthetised monkeys (Macacca fascicularis) to see if the inhibitory effect of indomethacin was reversible. Exogenous prostaglandin (PGE_2) infusion resulted in a marked calciuretic response without producing changes in GFR or blood pressure.

Selected hypercalciuric patients were treated with indomethacin, which resulted in a significant fall in urinary calcium excretion ($P < 0.001$). This clinical and experimental study suggests that PGE_2 is the hormone which determines the renal handling of calcium by controlling renal tubular function.

Hypercalciuria is well recognised as an important factor in the causation of idiopathic calcium urolithiasis. It is said to result from 2 major metabolic disorders: an increased intestinal absorption of dietary calcium (Peacock and Nordin, 1969; Pak *et al.*, 1974) and a renal leak or failure of tubular reabsorption of urinary calcium (Coe and Kavalach, 1974). Identification of the exact mechanism for the renal tubular handling of calcium has proved elusive and treatment methods to alter the concentration of urine calcium have hitherto been non-specific. In the clinical study herein reported, we observed that hypercalciuric patients had significantly higher GFR values when compared with normal subjects. This led us to consider the possibility that renal prostaglandins which regulate renal haemodynamics in some circumstances may be responsible. This study comprised 3 parts:

1. A clinical investigation of 275 idiopathic stone formers.
2. Experimental studies in conscious rats and anaesthetised monkeys to investigate the influence of endogenous prostaglandin activity on renal tubular calcium excretion.
3. A preliminary study of selected hypercalciuric patients treated with indomethacin.

Methods

Clinical Study

Two hundred and seventy-five patients with idiopathic calcium stones were studied; there were 232 males and 43 females whose ages ranged from 18 to 82 years. A diagnosis of stone disease was made on the basis of radiographic evidence and/or clinical criteria. The following were judged to be definite evidence of a calculus: visualisation of a stone by X-ray; passage of a calculus that was not previously visualised; typical renal colic localised to one side with microscopic and chemical haematuria. The patients were assessed to exclude specific causes of/or disorders associated with hypercalciuria and renal lithiasis.

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Investigations

Serum calcium, inorganic phosphate and uric acid were assayed on 3 occasions. Three 24-h urinary calcium concentrations were measured on consecutive days (hypercalciuria was defined by urinary calcium excretion >7.5 mMol/d^{-1} in males and >6.8 mMol/d^{-1} in females). Creatinine clearance was measured for 3 days. The patients were instructed in the appropriate method of urine collection and blood samples were taken between 0800 and 0930 h at the conclusion of each urine collection. Gastrointestinal absorption of calcium was measured by an arm counting technique following separate intravenous and oral doses of calcium 47 chloride (MacLeod, 1971). (The normal amount of oral calcium 47 absorbed from the intestine is <40%.)

An isotope study of renal function using ^{99m}Tc DTPA (Sn) enabled renal scintigraphy, renography and an isotope clearance (GFR), using an arm counting technique, to be performed.

Experimental Study

(a) Rats Experiments were performed on male rats (Sprague-Dawley strain, N = 6) weighing 250 to 400 g. Each rat was lightly anaesthetised with ether and a flexible cannula implanted into the tail vein (Lote and Snape, 1977). The animal was placed in a perspex restraining cage and allowed to recover from the anaesthetic. A constant infusion of NaCl 0.9% was begun into the tail vein at a rate of 5.8 ml/h and the infusion continued for 6 h. Urine samples were collected at 2 h and thereafter at hourly intervals throughout the 6-h infusion period. The animals received indomethacin (10 mg/kg) in buffered saline via the tail vein given over 15 min, beginning at 3 h 52 min.

(b) Monkeys Experiments were performed on anaesthetised monkeys (Macacca fascicularis, N = 4) to determine if the inhibitory effect of indomethacin on calcium excretion was reversible by an intra-arterial infusion of prostaglandin PGE$_2$. The animals were anaesthetised with intravenously administered pentobarbitone sodium (25 mg/kg) and maintained in a light plane of surgical anaesthesia. An intravenous injection of 1 mCi of ^{99m}Tc DTPA (Sn) was given to the animal and the renal clearance of the isotope continuously monitored throughout the experiment by means of a cadmium telluride detector placed over the chest. Polyethylene catheters were inserted into the femoral vein and femoral artery; the tip of the arterial cannula was sited in the aorta to lie proximal to the origin of the renal arteries. Saline 0.9% was infused through the intravenous catheter at a rate of 3.5 ml/min throughout the course of the experiment. Saline 0.9% was infused through the arterial cannula by means of an infusion pump to deliver infusate at a rate of 0.3 ml/min.

The intra-arterial cannula was coupled to an Elcomatic EM750 pressure transducer for continuous monitoring of blood pressure which was recorded on an RAF patient monitoring system Type IV with heart rate and BP meter.

Through a midline laparotomy incision bilateral ureteric polyethylene catheters were inserted for urine collection. The experiment was begun after 3 5-min urine volumes were stable within 0.5 ml from each kidney. Urine samples were collected at 30-min intervals; the first half-hour collection was taken as the control. Indomethacin (10 mg/kgm) was infused intravenously via the cannula in the femoral vein. One hour after the indomethacin infusion prostaglandin PGE$_2$ in a dose of 0.2 µg/kg/min was infused intra-arterially for a 30-min period. Urine was collected for a further half-hour period after the infusion of prostaglandin. Urine volumes, calcium and sodium excretion and creatinine clearance were measured in each 30-min collection.

Analytical Procedures for Urine

Urine sodium was determined by flame photometry using a Beckman flame photometer with lithium internal standard. Urine calcium excretion was measured by atomic absorption gas spectrometry.

Results

Results of the Clinical Study of 275 Stone Patients

In 148 patients (53.8%) urinary calcium excretion was elevated; mean urinary calcium excretion 11.29 ± SD 3.14 mMol/d. In the remaining 127 patients the mean urinary calcium excretion was 5.43 ± SD 1.31 mMol/d. Hypercalciuric patients had a higher incidence of recurrent stone formation (41.2%) compared with the normocalciuric patients (25.9%) together with a higher incidence of operative removal of the calculus. The clinical presentation of the hypercalciuric group compared with the normocalciuric group is shown in Table 1.

The radiological (IVU) findings in relation to

Table 1 Clinical Presentation in 275 Idiopathic Calcium Stone Patients

	Normocalciuric	*Hypercalciuric*
N	127	148
(Males)	(94)	(138)
(Females)	(33)	(10)
Mean age (years)	42.2±SD 13.4	40.6±SD 10.9
Duration of follow-up (years)	4.14±SD 3.94	5.32±SD 4.8
Mean urine calcium excretion mMol/24 h	5.43±SD 1.31	11.29±SD 3.14
Side of calculus		
Right	53 (41.7%)	60 (40.6%)
Left	64 (50.4%)	69 (46.6%)
Bilateral	10 (7.9%)	19 (12.8%)
Recurrent stone	33 (25.9%)	61 (41.2%)
Single stone (non-recurrent)	94 (74.1%)	81 (58.8%)
Operation for removal of stone	20 (15.7%)	34 (22.9%)

the clinical presentation of the stone are shown in Table 2. Hypercalciuric patients had an increased incidence of obstructive calculus requiring operative removal.

Of the 275 patients, 201 (73%) absorbed calcium excessively. One hundred and eight of the 148 hypercalciuric patients (73%) and 93 of the 127 normocalciuric patients (73%) showed an increased absorption of calcium 47 (greater than 40%); the extent of hyperabsorption of calcium was the same for both groups of patients.

An excellent correlation was observed between GFR measured by creatinine clearance and the T½ biol. of ^{99m}Tc DTPA (Sn) (r = 0.91). In this study creatinine clearance has been used to determine glomerular filtration rates and the results from the 2 groups of patients compared with GFR in 120 age-matched normal controls (Table 3). Hypercalciuric patients had a significantly increased GFR compared with the normal controls and normocalciuric stone formers (Figs. 1a, b, c). ^{99m}TC DTPA (Sn) scintigraphy in several urolithiasis patients showed areas of increased isotope density within the kidney corresponding to the site of a calculus or an area of parenchymal calcification. When these localised areas were selected as regions of interest and activity time curves generated, they were seen to represent areas of increased activity which suggested altered local haemodynamic function relative to other areas in the kidney.

Table 2 Results of Intravenous Urogram (IVU) Related to the Clinical Presentation in Normocalciuric and Hypercalciuric Stone Patients

	Normocalciuric	*Hypercalciuric*
Calculus causing obstruction	18 (14.17%)	33 (23.3%)
Operative removal	(9)	(20)
Spontaneous passage	(9)	(13)
Operation for removal of symptomatic (non-obstructing) calculus	11 (8.6%)	14 (9.4%)
Persisting parenchymal calcification	31 (24.4%)	38 (25.6%)
Normal IVU (after passage of stone)	67 (51.9%)	63 (42.56%)
Total	127	148 (100%)

Table 3 Correlation of GFR With Age in Normocalciuric and Hypercalciuric Patients Compared With Normal Control Subjects

GFR (creatinine clearance) correlation with age and clinical status

	N	*Mean age*	*GFR (ml/min)*	*SD*
(1) Normal subjects	120	40.4	101.8	±19.2
(2) Normocalciurics	119	42.8	99.5	±21.5
(3) Hypercalciurics	135	40.4	127.9	±24.1

(1) : (2) N.S.
(1) : (3) $P < 0.001$

The Results of Prostaglandin Synthetase Inhibition of Calcium Excretion in Rats (Sprague Dawley, N = 6)

The time course of the changes in urinary calcium excretion are shown in Figure 2. The initial 2 h of the infusion were regarded as an equilibration period during which time the urine flow increased to match (and usually exceed) the infusion rate, *i.e.* 96.7 µL/min); the urinary calcium output in the 2-h period before indomethacin administration was 0.34±SE 0.05 µmol/min; in the 2-h period after indomethacin this was reduced to 0.19±SE 0.04 µmol/min (paired "t" test $P < 0.002$, $N = 6$)(Fig. 3). Urinary sodium output also showed a decrease from 19.01±SE 1.11 µmol/min in the 2 h before indomethacin to 15.34±SE 0.99 µmol/min in the 2 h after indomethacin ($P < 0.05$).

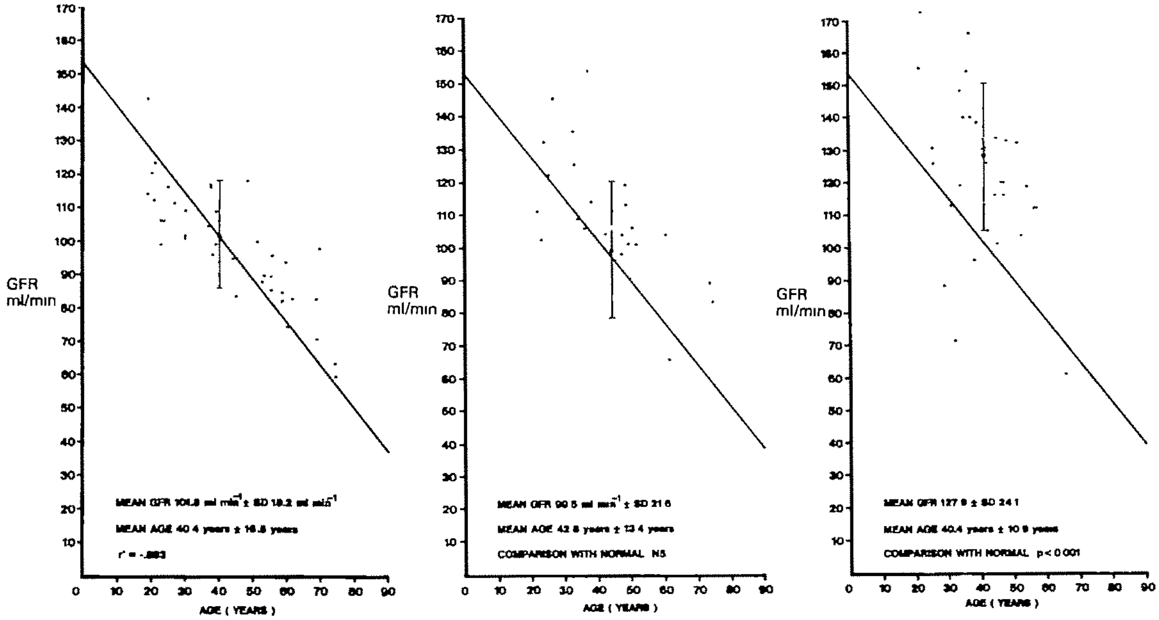


Fig. 1 (a) Regression of GFR on age in 120 normal subjects showing inverse correlation of GFR with age (r = −0.883). (b) Comparison of 119 normocalciuric stone formers against the regression line for normal subjects. (c) Comparison of GFR in 135 hypercalciuric patients compared with the regression line for normal subjects. Hypercalciuric stone formers show significantly increased GFR ($P < 0.001$).

Results of Prostaglandin Synthetase Inhibition and Prostaglandin Induced Calcium Excretion in Cynomolgus Monkeys (Macacca Fascicularis, N=4)

The infusion of indomethacin produced a decrease in urine flow and in calcium excretion in the 60-min period following indomethacin administration. Prostaglandin PGE_2 infusion resulted in a marked calciuretic response in all of the animals for the 30-min period during the continuous intra-arterial infusion of PGE_2. Calcium excretion returned to normal in the 30-min period following PGE_2 administration (Fig. 4).

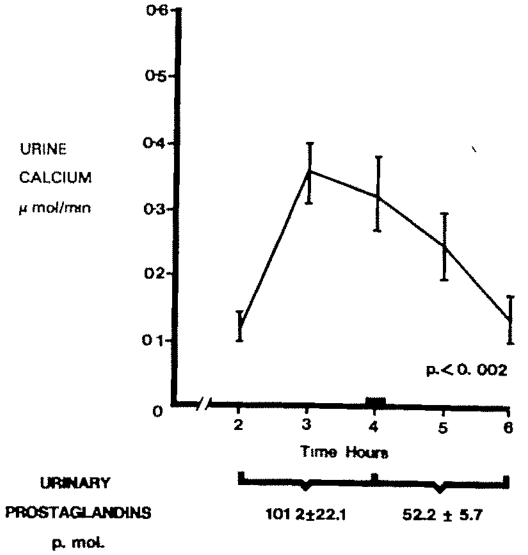


Fig. 2 Urinary calcium output in 6 experimental rats. The animals received indomethacin (10 mg/kg) over 15 min (indicated by bar). Values reported are mean ± SE of mean. There was a significant fall in calcium excretion with indomethacin (paired "t" test $P < 0.002$).

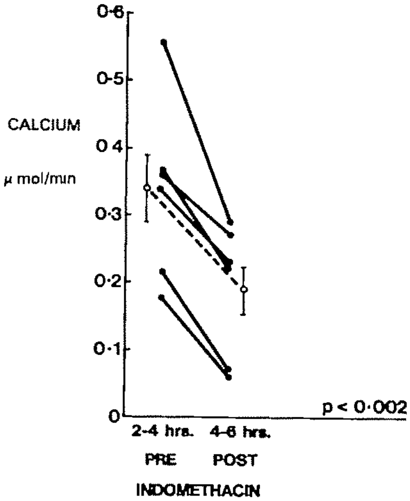
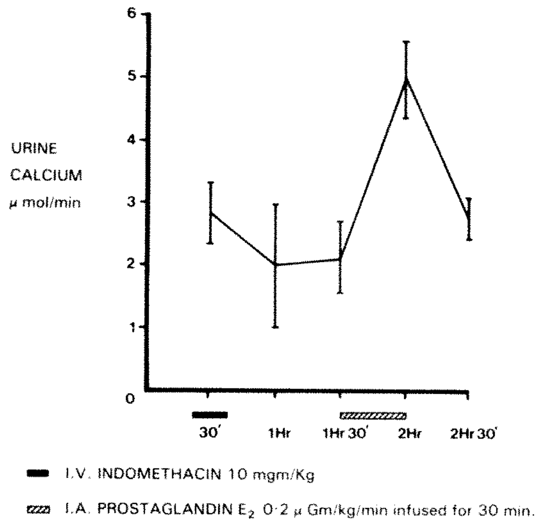


Fig. 3 Mean urinary calcium output for 2-hr periods before and after indomethacin. (Values are mean ± SE of mean.)



99m Tc DTPA CLEARANCE ml/min	1. 15·4	10·3	12·9	14·7	14·6
	2. 13·0	12·1	13·5	12·8	12·8
	3. 14·6	14·3	13·9	14·8	13·9
	4. 13·94	13·95	13·31	15·22	15·33
MEAN	14·23±1	12·6±1·8	13·4±0·4	14·38±1	14·15±1

Fig. 4 Urinary calcium output in 4 anaesthetised monkeys showing a fall in urinary calcium output with indomethacin and increased calcium excretion with intra-arterial infusion of exogenous PGE_2. (Values plotted are mean ± SD of mean.)

There was a slight fall in ^{99m}Tc DTPA (Sn) GFR clearance with indomethacin but no change was seen with PGE_2 infusion.

The mean blood pressure was within the range of 110-125 mmHg and there were no significant differences between the periods of indomethacin and prostaglandin infusion at any time during the experiments.

Treatment of 11 Hypercalciuric Patients with Indomethacin

On the basis of the results of these animal experiments it was decided to study the effect of indomethacin on urinary calcium excretion in a group of 11 hypercalciuric, recurrent stone formers: 24-h urinary calcium excretion was measured on 3 occasions prior to treatment with indomethacin (25 mg tid). Following a period on treatment for 10 days, three 24-h urinary calcium excretions were again measured. The mean pre-treatment 24-h calcium excretion was 10.32 ± SE 0.56 mMol/ d^{-1} but fell significantly to 6.32 ± SE 0.43 mMol/ d^{-1} with indomethacin administration (unpaired "t" test $P < 0.001$, $N = 11$) (Fig. 5).

Discussion

An increased alimentary absorption of dietary calcium is generally regarded as the main metabolic abnormality responsible for idiopathic hypercalciuria (Peacock *et al.*, 1967; Coe *et al.*, 1973; Pak *et al.*, 1974). However, a direct relationship is unlikely since the same proportion of hypercalciuric and normocalciuric patients were calcium hyper-absorbers. In this study a notable observation was the significantly increased GFR in hypercalciuric stone formers, which prompted the enquiry as to whether the association was coincidental or a true causal relationship. Calcium transport from tubular lumen to peri-tubular blood prevents the large amounts of calcium filtered at the glomerulus (about 8-10 g/d) from being excreted in the urine: thus both the filtered load of calcium, which is partly GFR dependent, and tubular reabsorption are important interrelated aspects of renal function in hypercalciuria.

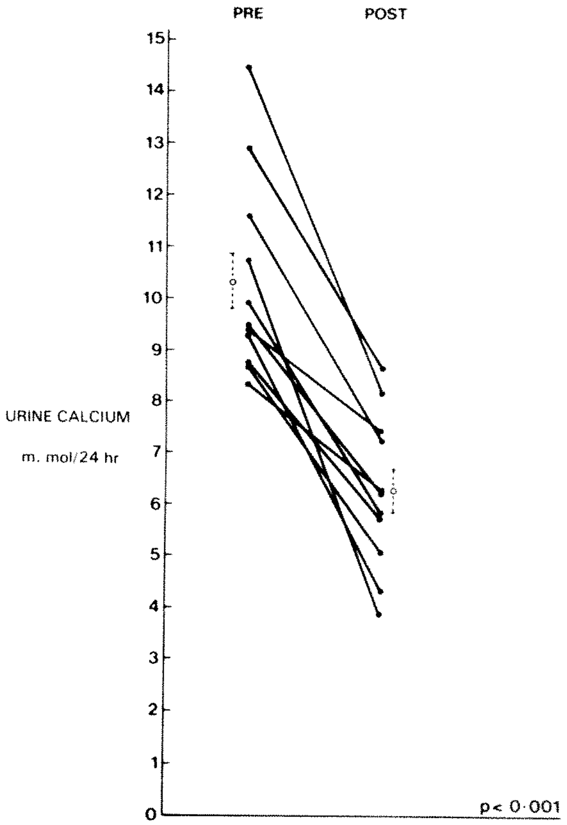


Fig. 5 Effect of indomethacin on urinary calcium excretion in 11 hypercalciuric stone formers. Mean values of three 24-h urinary calcium excretions are represented for each patient before and after indomethacin (unpaired "t" test $P < 0.001$).

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In this study the differences in GFR became apparent when the factor of age dependency with respect to renal clearance was taken into account. Hodgkinson and Heaton (1965) showed that the ingestion of food caused a marked increase in glomerular filtration coincidental with an increased urinary calcium excretion and ascribed this to an increased filtered load. While the implications of these findings are that of a general metabolic response to nutrient ingestion, it is also necessary to consider that this could be due to regional alterations in renal blood flow dependent on a local stimulus. Further support for a focal rather than a generalised stimulus to increased glomerular filtration derived from our experience of the dynamic scintigram in renal stone formers. Our attention was drawn to the consistency of localised areas of increased isotope density corresponding to the site of the stone, a previous stone, or nephrocalcinosis, which were initially interpreted as areas of stasis or obstruction (Buck *et al.*, 1980). However, with improved techniques of selective renography these areas were found in many instances, to represent areas of enhanced localised functional activity and clearance in the renal parenchyma and not obstruction.

The prostaglandins are important intra-renal hormones concerned with the regulation of renal blood flow and electrolyte excretion by the kidney (Lee, 1974; Anderson *et al.*, 1976; Frolich *et al.*, 1981). Until recently these 2 important homeostatic functions were thought to be interdependent, with sodium excretion occurring secondarily to changes in blood flow and water diuresis (McGiff and Malik, 1976; Berl *et al.*, 1977). Haylor and Lote (1980) provided evidence for a direct tubular action of endogenous prostaglandin on distal nephron sodium excretion and showed that this effect could be inhibited by indomethacin, independent of changes in renal plasma flow and GFR.

Investigations into the renal action of prostaglandins have hitherto been confined to sodium and potassium excretion, the regulation of renin secretion, renal haemodynamics and water diuresis (Weber *et al.*, 1979). There have been no previous studies with respect to the influence of prostaglandin on the renal handling of calcium. In view of the intimate relationship between the tubular transport of calcium and sodium, the possibility that hypercalciuria and GFR changes in urolithiasis could be prostaglandin-mediated needed to be considered. There is also good circumstantial evidence to suggest that prostaglandins may influence calcium reabsorption by the kidney as prostaglandins have been shown to alter water, sodium and calcium transport across frog skin (Lote *et al.*, 1974). More significantly, indomethacin has been effective in normalising the severe hypercalciuria associated with Bartter's syndrome and congenital tubulopathies (Donker *et al.*, 1977; Betend *et al.*, 1979).

The present findings in conscious rats confirm the changes in renal excretion of water and sodium following prostaglandin synthetase inhibition with indomethacin (Haylor and Lote, 1980). In addition we have demonstrated that endogenous prostaglandin determines the renal excretion of calcium, which was significantly reduced following indomethacin administration.

As indomethacin inhibits the cyclo-oxygenase synthesis of prostaglandin from arachidonate and is without effect on prostaglandins themselves, experiments were carried out in anaesthetised monkeys to show that the inhibitory effect of indomethacin was reversible by exogenous prostaglandin infusion. The striking calciuretic response with PGE_2, independent of changes in GFR and blood pressure, suggests that this renal prostanoid determines the renal handling of calcium by controlling tubular function.

The marked reduction in urinary calcium excretion with indomethacin in hypercalciuric patients in this preliminary study is further evidence that renal prostaglandin activity is an important factor in the mechanism of hypercalciuria which hitherto has not been recognised. Further studies are in progress to clarify the role of prostaglandins in the pathogenesis of stone formation within the kidney and to establish whether prostaglandin synthetase inhibition with non-steroidal anti-inflammatory drugs will be the specific treatment for hypercalciuria.

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^{99m}Technetium DMSA and the Prediction of Recovery in Obstructive Uropathy

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Summary—Predictions of the potential for recovery of renal function in obstructive uropathy are difficult and unreliable. ^{99m}Technetium DMSA accumulates in tubule cells and has been proposed as a marker of the tubular mass. However, in 34 patients with obstructive uropathy we have found no correlation between the pre-operative scintigraphic appearances of the obstructed kidney and the post-operative result. Reduced or absent DMSA uptake does not necessarily mean irreversible renal damage.

Obstruction in the urinary tract is still primarily diagnosed by a well-performed excretion urogram in most cases. To supplement this, and in special situations, isotope renography using DTPA or Hippuran with modifications such as induced diuresis (O'Reilly *et al.*, 1978) or deconvolution analysis (Britton *et al.*, 1979; Buck *et al.*, 1980) may be useful, as are pressure flow studies in equivocal cases (Whitaker, 1976).

Obstruction eventually results in damage to the kidneys and loss of function. The questions that concern the clinician are the degree of nephron loss in that kidney and the potential for recovery following the relief of obstruction. The intravenous urogram (IVU), though a primary diagnostic procedure, remains a qualitative examination and does not accurately indicate the functional mass of each kidney. Predictions of recovery in obstructive uropathy are unreliable (Chisholm, 1974) and none of the above methods or their variations can indicate this potential.

Earlier studies of renal functional mass used mercurous chloride labelled initially with ^{203}Hg and later with ^{197}Hg. Although a $^{197}HgCl_2$ renal uptake test is an accurate quantitative renal functional test, the radiation dose absorbed by the kidneys and other drawbacks of this isotope have limited its use (Chisholm *et al.*, 1967; Taylor and Nelson, 1979). In 1975 Arnold *et al.*, evaluated a large number of technetium labelled materials suitable for selective renal uptake and concluded that dimercaptosuccinic acid (DMSA) had the best characteristics for renal imaging. The renal uptake level reaches a plateau around the tenth hour, then represents approximately 30% of the dose. Urinary excretion varies from 15 to 20% of the dose in the first 24 h. Further reports have documented the role of this agent in detecting abnormalities of and its correlation with renal function (Kawamura *et al.*, 1978) and established the optimal criteria for its use (Daly *et al.*, 1978). Applying the methods of frozen section autoradiography to kidneys, Willis *et al.* (1977) concluded that ^{99m}Tc DMSA accumulates in the cytoplasm of the proximal tubule cells in the inner renal cortex, where it has recently been shown to bind mostly to cytosol proteins and to mitochondria and to a lesser extent to nuclei and microsomes (Vanlic-Razumenic and Petrovic, 1981). This would tend to support the observation by Kawamura *et al.* (1978) that by measuring the DMSA uptake, cortical functional nephrons could be determined independent of urinary flow rate and that DMSA was acting as a cortical tubular cell marker.

Patients and Methods

Since 1978 most of our patients with obstructive uropathy have been examined by DMSA scans before and after relief of obstruction. Thirty-four patients have had serial DMSA examinations to assess relative uptake (RU) before and after the relief of unilateral obstruction, the aetiology of which is noted in the Table.

Technetium-dimercapto-succinic acid (DMSA) (C.I.S., France) was injected in a dose of 3 to 4 mCi. One and a half to 4 h after injection, 400,000 counts were collected from the posterior

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table Aetiology in 34 Cases of Unilateral Obstruction

14	Congenital pelviureteric junction obstruction
15	Pelvic or ureteric stones
4	Ureteric strictures
1	Trauma

view for differential renal function analysis. The patient was usually seated unless the kidneys were mobile and low, in which case a supine view was preferred. In the case of mobile or low kidneys it is preferable to perform anterior and posterior view scans and to calculate the geometrical mean of the 2 values.

An Ohio Nuclear-Sigma 100 gamma-camera was used with a standard general purpose collimator. Data were analysed by a Varian V-72 computer and used to calculate the activity of each kidney which was then expressed as a percentage of the total uptake.

Results

Twenty of the 34 patients studied had significantly reduced relative uptakes on the obstructive side (*i.e.* <45%). Of these, 19 cases have shown improvement following relief of obstruction. The effect appeared most dramatic in 3 cases where the relative uptake of the obstructed kidney was less than 10%.

Case 1. Mrs S.M. presented with a right renal calculus. The excretion urogram showed no function in the right kidney up to 17 h (Fig. 1) and there was no detectable uptake of DMSA on the right (Fig. 2). However, at exploration the right kidney, though grossly dilated, had reasonable cortical thickness. Nephrectomy was decided against and a pyelolithotomy was carried out. A biopsy of the renal cortex showed viable tubules with a scattered interstitial inflammatory exudate. DMSA scans in the post-operative period showed some evidence of recovery which gradually increased to 18% in one year and reached 24% at 3 years (Fig. 3). An intravenous urogram after one year showed a dilated right pelvicaliceal system (Fig. 4).

In most of the cases there was a significant improvement as early as 15 to 30 days after obstruction had been relieved, followed by a slower and prolonged recovery over as long as 3 years. The following is an example of one such case.

Case 2. Mr J.S. presented with a left-sided renal stone and a DMSA study showed relative uptake of 25% on the right side. Ten days following the removal of the stone a repeat DMSA study showed that the relative uptake of the right kidney had increased to 48%.

In 14 cases, the function of the obstructed kidney was not significantly reduced (*i.e.* >40%) and in 9 of these the obstructed kidney contributed more than 50% of the total uptake. These cases fell into 2 groups: (1) where the contralateral kidney was indeed smaller, possibly

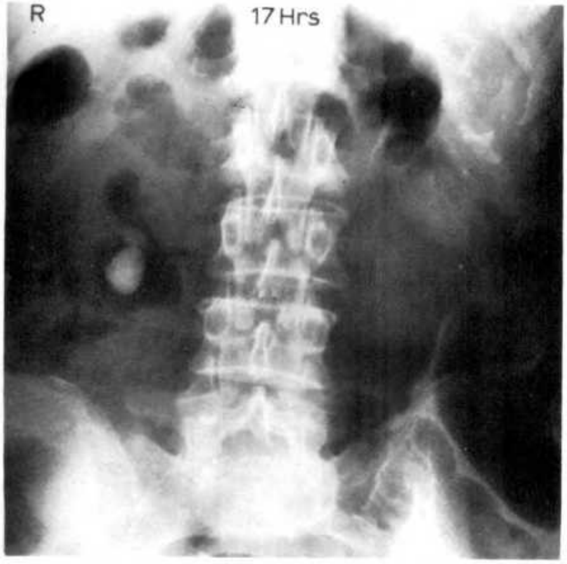

Fig. 1 Case 1. Intravenous urogram showing no function of the right kidney at 17 h.

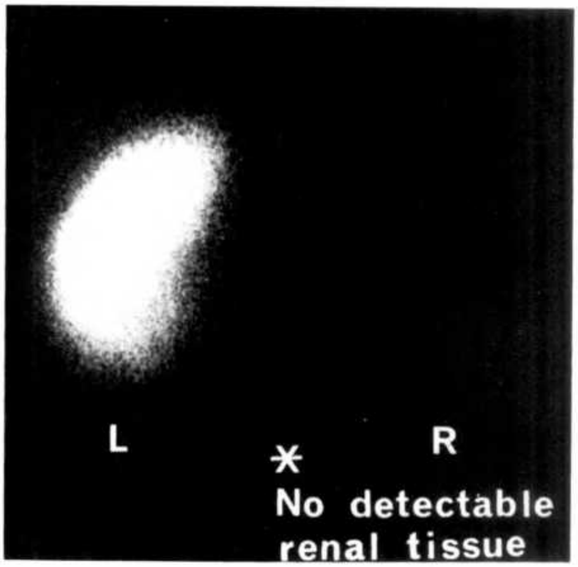

Fig. 2 Case 1. DMSA scan showing no uptake of radioisotope by the right kidney.

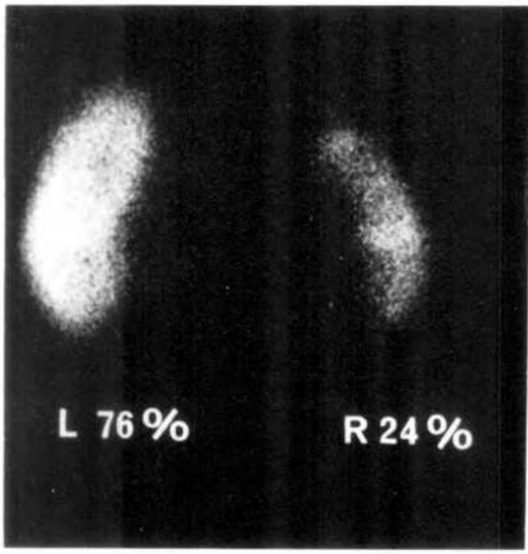

Fig. 3 Case 1. DMSA scan 3 years after relief of the obstruction. Right kidney now contributes 24% of renal function.

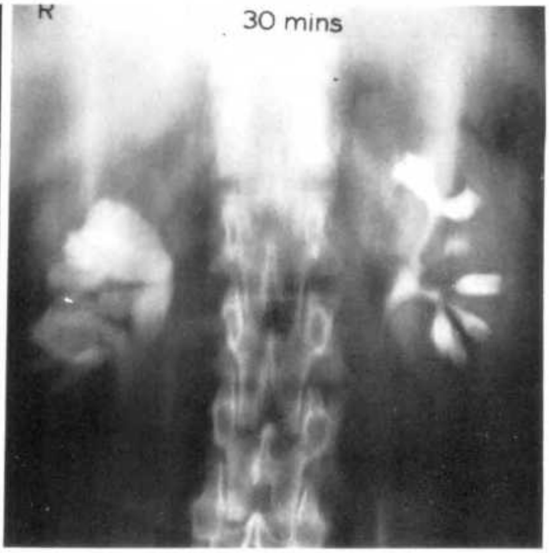

Fig. 4 Case 1. Intravenous urogram one year after relief of obstruction showing prompt excretion at 30 min.

scarred by previous infections and therefore the obstructed kidney, despite its handicap, contributed more than 50% of the total uptake; (2) a falsely elevated renal uptake due to the contribution of excreted isotope retained within the dilated collecting system. This error can be overcome by performing a late picture (*i.e.* 18-24 h after injection) as shown in the following case:

Case 3. Mr F.H. presented with left-sided loin pain and an excretion urogram confirmed left hydronephrosis secondary to a pelviureteric junction obstruction. A DMSA study 3 h after the injection showed a relative uptake of 55% on the left side. The scintigraph image was suggestive of concentration of activity in the extra-renal pelvis and therefore repeat pictures were performed at 24 h. This showed that the left kidney contributed 47% of total uptake.

In a few cases, however, neither of the above reasons was applicable, and the cause of increased uptake on the obstructed side remained uncertain. It may be due to hyperaemia, which often accompanies acute obstruction.

Discussion

Having made a diagnosis of obstructive uropathy, the clinician would then wish to prognosticate regarding the chances of functional recovery of that kidney once the obstruction was relieved. Radioisotope tests that differentially calculate the GFR, the ERPF and other such measurements of each kidney are available. However, these values are greatly dependent on urinary flow and are significantly, albeit temporarily, depressed as a result of obstruction. Therefore, although they can accurately indicate the function of the obstructed kidney, they give no indication of the potential for recovery in that kidney.

Kawamura *et al.* (1978) felt that DMSA should be used for labelling the functioning nephrons in the cortex, regardless of urinary flow, because it is a cortical tubular marker. They noted that when the DMSA uptake was 0% the extirpated kidney showed almost no parenchyma and histologically functioning nephrons were not apparent. Experience from the present study differs. We would challenge the statement that no DMSA uptake (or very poor DMSA uptake) always means no cortex (or very little cortex). In practice, these kidneys often have a substantial amount of cortical tissue which can recover. We therefore deduce that although the DMSA scan is an indicator of the functioning tubular mass *at the time of the study*, following relief of obstruction, uptake may improve within a few weeks; it is not an absolute indicator of the amount of viable renal tissue in the presence of urinary obstruction. A prediction of recovery after relief of obstruction based on a single DMSA scan is not justifiable and may be misleading.

Contrary to the view held by some workers, activity in the renal pelvis urine does in some cases give rise to a false elevation in relative uptake on that side. Therefore, although in most cases scintigraphy 1½ to 4 h after injection is satisfactory and certainly more acceptable from the patient's point of view, the occasional case will require late views at 18 to 24 h (see Case 3).

It is concluded from the present study that the distinction between functioning and potentially functioning renal mass remains the major unsolved problem in obstructive uropathy and nephropathy. However, DMSA scintigraphy is a simple, reproducible method of following the recovery of a kidney after successful relief of obstruction. In practice, it has been found that in the follow-up of patients treated for their urinary obstruction, the use of serial DMSA studies to assess tubular mass and DTPA renograms to exclude persistent or recurrent obstruction have almost eliminated the need for repeated urograms.

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The Predictive Accuracy of Antegrade Pressure Flow Studies in Equivocal Upper Tract Obstruction

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Summary—Twenty-one of 27 antegrade pressure flow studies performed before 1973 have been reviewed at a minimum of 5 years to assess the predictive value of the studies. There is no case in this series that has suggested that the incorrect information was supplied at the initial investigation.

Antegrade pressure studies are of proven value in the diagnosis of obstruction in the upper urinary tract due to conditions such as pelviureteric junction obstruction, retroperitoneal fibrosis and megaureter (Whitaker, 1975a and b; Pfister and Newhouse, 1979). Of great interest is the possible value of these studies in predicting the course of renal function and changes in urographic appearances in the dilated upper urinary tract over a long period of time. We have reviewed our earlier perfusion studies to see what the eventual outcome was some years later.

Patients and Methods

Four adults (age range 26-45 years) and 23 children between 3 days and 14 years old (mean 2.8 years) with dilated upper tracts were reviewed. Obstruction was suspected in all patients and the diagnoses are shown in Tables 1 to 4. Antegrade perfusion studies by percutaneous puncture, nephrostomy or direct measurement at operation had been performed to confirm or exclude obstruction at some time between 8 and 10 years ago by the method previously described (Whitaker, 1973, 1979b). The renal pelvic pressure minus bladder pressure is described as relative pressure (RP). RP for each study at a flow rate of 10 ml/min is shown in Tables 1 to 4. An RP of more than 15 cm H_2O was considered elevated.

Twenty-one of these cases have been followed for over 5 years and renal function has recently been assessed by serum creatinine and renal isotope studies where possible and the appearances of the urinary tract by intravenous urography (IVU).

Results

The results of the studies can be categorised into 4 groups:

Group A An elevated relative pressure was found and this was followed by a corrective operation.

Eleven cases had relative pressures of between 16 and 150 cm H_2O at a perfusion rate of 10 ml/min. Eight were thought to be cases of primary obstructed megaureter, 2 of pelviureteric junction obstruction and there was one case of hydroureteronephrosis secondary to posterior urethral valves. The appropriate operation was performed (Table 1).

Eight patients were seen between 8 and 10 years later. In 2 of these cases (VL, MR) the IVU was similar but function was stable, while in the other 6 the IVU showed less dilatation and there was evidence of renal growth. Serum creatinine was improved or stable in all of these patients. The other 3 patients were reviewed between 2 and 4 years later, when improvement was noted in both radiological appearance and in renal function.

Group B An elevated relative pressure was followed by no operation.

Despite elevated pressure differences in 2 cases (Table 2) of 106 (ML right) and 25 (DG) cm H_2O, no surgery was performed. In the first patient the IVU appearances deteriorated 4 years later and led to a trans-ureteroureterostomy (ML's left RP was not elevated), after which the appearance of this kidney stabilised. DG's function deteriorated steadily over the years, his serum creatinine being

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Table 1 Group A

Number	*Case*	*Age*	*Diagnosis*	*RP*	*Operation*	*Outcome*		
						Yrs	*CR μmol/l*	*IVU*
1	SC		PUJ	23	Pyeloplasty	5		Improved
2	MS	41	PUJ	40	Pyeloplasty	5	100	Improved
3	VL	26	L. megaureter	19	Boari Flap, TUU*	6	87	Stable
4	AP	6	L. megaureter	16	Reimplant	5		Improved
5	JT	2	L. megaureter	140	Reimplant	5	50	Improved
6	RR	14	L. megaureter	100	Reimplant	2	55	Improved
7	NN	1	R. megaureter	40	Reimplant	2		Improved
8	SC	6	Bil megaureter	30	Reimplants	4	44	Improved
9	AO	1½	Bil megaureters	20	Reimplants	8	60	Improved
10	MD	1	Bil megaureters	R36 L34	Reimplant	8	50	Improved
11	MR	6	Valves + dilatation	25	Reimplant	8	40	Stable

*TUU = Transureteroureterostomy.

640 μmol/l 8 years later and he has eventually required a renal graft.

In 2 patients in this group the RP was not elevated but the renal pelvic pressure rose on bladder filling to 32 (RO'H) and 67 (DF) cm H_2O. Renal function has deteriorated in both of these children, their serum creatinines being over 350 μmol/l 9 years later. It is of note that DF's creatinine fell during a brief period of bladder drainage, although a urodynamic study of his outflow tract excluded obstruction.

A further case in this group is of special interest. PD presented with posterior urethral valves and bilateral hydroureteronephrosis. When a pressure study was performed RP was 20 cm H_2O and the pressure in the bladder rose to 30 cm H_2O when it was filled. No ureteric operation was performed and 3 years later his IVU showed improved appearance of the upper tracts. This study was performed shortly after the resection of his valves and it is likely that the initial hypertonicity of the bladder has settled.

Group C A low relative pressure was found and no operation performed.

In 7 of these cases with dilated upper tracts and a variety of diagnoses (Table 3), obstruction was excluded by an RP of 15 cm H_2O or less and no operation was performed. This inactivity appears justified, for at follow-up between 5 and 9 years later all have unchanged IVU appearances and stable renal function.

Group D A low relative pressure was found and despite this an operation was performed.

Table 2 Group B

Number	*Case*	*Age*	*Diagnosis*	*RP*	*Operation*	*Outcome*		
						Yrs	*CR μmol/l*	*IVU*
1	DG	10	Valves	25	None	8	640	Worse (transplant)
2	DF	3/7	Valves	7 (bp* 60)	None		374	Worse
3	ML	3	Valves R. dilatation Post. right implant	106	None	4		Worse (TUU† to left)
4	RO'H	14	Ectopia Variant	7 (bp* 25)	None	8	440	
5	PD	2	Valves	20 (bp* 30)	None	2		Improved

* bp = Bladder pressure.
†TUU = Transureteroureterostomy.

Table 3 Group C

Number	*Case*	*Age*	*Diagnosis*	*RP*	*Operation*	*Outcome*		
						Yrs	*CR µmol/l*	*IVU*
1	DD	5	Valves	11	None	8	70	
2	ML	3	Valves L. dilatation	11	None	8	80	L. stable
3	MA	2	Valves, remodel R.	4	None	7	70	
4	JM	3	Valves, dilatation	9	None	7		Improved (BU 5.7 mmol/l)
5	JB	45	Megacystis Megaureter	7	None	5		Unchanged
6	AJ	38	Ureterocolic anastomosis	15	None	8		Unchanged
7	MB	2ms	Post R. reimplant (Reflux)	10	None	9	93	

In 4 cases (Table 4), despite a low RP at perfusion study (3-15 cm H_2O), an operation was undertaken to relieve what were independently thought to be obstructed megaureters. It must be recalled that perfusion studies were a relatively new and untried method of investigation at that time and these cases were thought to be obstructed on clinical and radiological grounds. The IVU appearances were unchanged in 3 of these patients between 5 and 8 years after their operations and renal function had not been improved significantly. Follow-up was only at one year in the fourth patient, when his function and IVU were as before.

Discussion

Antegrade pressure studies have proved accurate in predicting the outcome in any particular patient.

Where the relative pressure was elevated, improvement in the upper tract was seen following an operation to relieve the obstruction. It is interesting to note one child with a megaureter (AP) has an RP of only 16 cm H_2O, yet the radiological appearance improved following a reimplant. This supports the view that 15 cm H_2O is the critical RP and that higher values signify obstruction.

When the RP was elevated and an operation was delayed, deterioration occurred. Function also deteriorated when the RP was not elevated but the total renal pelvic pressure was elevated (DF and RO'H) as a result of a hypertonic bladder. These cases demonstrate the importance of measuring the pressure in the bladder which can be reflected in the renal pelvis during diuresis (Struthers, 1969) or in the dilated upper tract. This vesical pressure does not always fall to a safe level following relief of the obstruction to the outflow of the bladder and represents a residual hypertonicity. Further evidence for this pressure being at fault is shown by the fall in serum creatinine on draining the bladder in one of these cases (DF). The management of this type of bladder presents considerable difficulty

Table 4 Group D

Number	*Case*	*Age*	*Diagnosis*	*RP*	*Operation*	*Outcome*		
						Yrs	*CR µmol/l*	*IVU*
1	FP	8	L megaureter	3	Reimplant	5		Unchanged
2	TH	11	L. megaureter	8	Reimplant	1	40	Unchanged
3	AR	9	Bil megaureter	R15 L12	Reimplants	8		Unchanged (GFR same)
4	RB	9	Bil megaureter	R10 L14	Reimplants	5		Unchanged

and one may be forced to perform a surface diversion.

PD is of interest in that despite an elevated RP and vesical pressure, his upper tract appearances eventually improved. This urinary tract was studied a short time after the relief of the obstruction to the outflow of his bladder, when the bladder itself was still hypertonic. This must have subsequently improved, with a decrease in vesical pressure and RP.

When RP is below 15 cm H_2O, without elevation of the pressure in the bladder, renal function did not deteriorate in a single case. Surgery for these low pressures is unnecessary, as shown by the failure of any of these cases that were operated upon to improve.

This review has demonstrated that it is the child with posterior urethral valves and dilated upper tracts that presents the greatest challenge in the prediction of the future course of renal function. Antegrade perfusion studies can elicit the rare secondarily obstructed ureterovesical junction which requires reimplantation, and combined with measurement of the pressure in the bladder can demonstrate an upper tract that is particularly likely to be at risk in the long term.

The series has also illustrated the existence of non-obstructed megaureter and that dilatation of the upper tract can be gross with no evidence of obstruction.

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Renal Transit Time Measurements in the Diagnosis of Ureteric Obstruction

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Summary—Deconvolution analysis of the gamma camera renogram has been used in a prospective study of 60 cases presenting with radiologically demonstrated ureteric dilatation.

The results show that ureteric dilatation due to obstruction can be differentiated from ureteric dilatation without obstruction on the basis of parenchymal tracer transit times.

Whenever a dilated upper urinary tract is demonstrated radiologically the question that faces the urologist is whether the dilatation is due to a significant degree of obstruction. This dilemma is found in both paediatric and adult urological practice and there are few topics which, in recent years, have attracted more controversy or interest.

Radiological studies alone may be diagnostic, particularly if the suspected site of obstruction is at the pelviureteric junction; however, even here there are cases in which it is not possible to make a radiological diagnosis and the lower down the ureter the suspected site of obstruction, the more difficult it becomes on radiological grounds to differentiate a dilated obstructed from a dilated but non-obstructed system.

Pressure/flow studies have helped to refine the diagnosis (Whitaker, 1979), but the technique is not without its problems (Whitfield *et al.*, 1976; Coolsaet *et al.*, 1980).

Standard probe renography is an unsatisfactory method of diagnosing obstruction, since it is not possible to differentiate a continuously rising second phase due to a mixing effect of tracer in a dilated but unobstructed system from a continuously rising second phase due to a true obstruction. Diuresis renography has been described in an attempt to overcome this problem and the technique correlates well with other methods of diagnosing obstruction (O'Reilly *et al.*, 1978).

We have previously reported the results of radionuclide imaging with a gamma camera in the diagnosis of pelviureteric junction obstruction (Whitfield *et al.*, 1977, 1978). Parenchymal tracer handling is separated from the passage of tracer through the collecting system using region of interest selection from a "mean time" functional image. From each activity/time curve, tracer transit timers can be quantified by deconvolution analysis.

This paper reports the results of a study in which the technique of deconvolution analysis of the gamma camera renogram was applied to patients with radiologically demonstrated ureteric dilatation.

Patients and Methods

Sixty kidneys in 48 patients were studied. There were 18 females and 30 males whose ages ranged from 15 to 71 years, with an average age of 43 years.

The causes of the ureteric dilatation are shown in Table 1.

Table 1 Causes of Ureteric Dilatation

Diagnosis		*No. of patients*
Stones		19
Congenital disorders		8
Fibrosis—post-operative	5	
—paracolic abscess	1	6
Ureteroileal stenosis		5
Carcinoma—prostate	2	
—colon	1	
—ureter	1	4
Tuberculosis		2
Radiotherapy		2
Benign RPF		1
Bladder neuropathy		1

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Table 2 Patient Groups

	No. of cases
A. Renographically obstructed initially who underwent conservative surgery or passed a stone	16
B. Renographically obstructed initially who were managed conservatively	11
C. Renographically unobstructed	25
D. Renographically equivocal	5
E. Renographically obstructed who underwent ablative surgery or died	3

The patients were divided into 5 groups (Table 2).

The radiopharmaceuticals used were either ^{99m}Tc DTPA or ^{123}I-Hippuran in a dose of 10 to 15 mCi and 2 mCi respectively. The details of the computer techniques employed have been described previously (Britton *et al.*, 1979; Nimmon *et al.*, 1981).

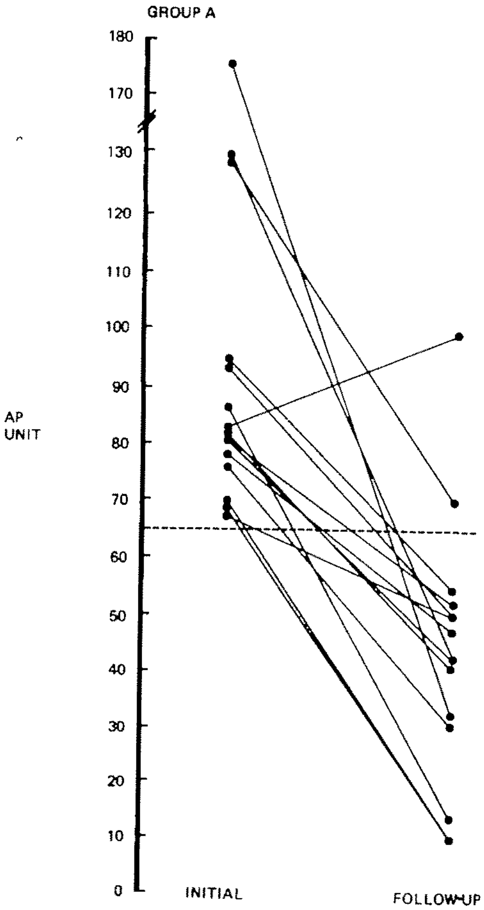

Fig. 1 Results of parenchymal transit times in patients presenting with renographic evidence of obstruction who underwent conservative surgery or who passed a stone spontaneously.

Results

Group A (Fig. 1)

Of the 16 patients who were renographically obstructed initially and who either underwent conservative surgery or passed a stone spontaneously, 15 have undergone serial gamma camera studies. One patient refused follow-up.

In 13 cases the parenchymal isotope transit time (PTT) returned to normal. In one patient who initially had a high PTT the level fell to 70 Ap units 3 months after the passage of a stone and further studies are awaited. In one patient who underwent ureterolithotomy there is clinical and radiological evidence of persisting obstruction which correlates with the persistence of a PTT in the obstructed range.

Group B (Fig. 2)

Eleven patients who presented with ureteric dilatation and renographic evidence of obstruction have been managed conservatively. Six of these

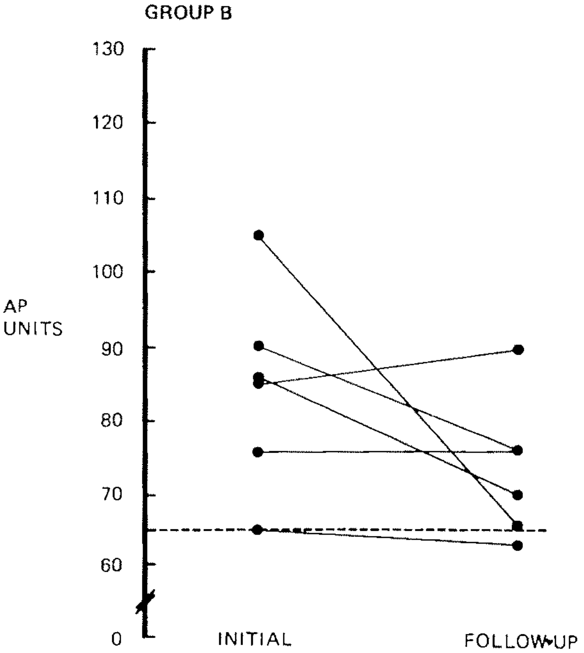

Fig. 2 Results of parenchymal transit times in patients presenting with renographic evidence of obstruction who were managed conservatively.

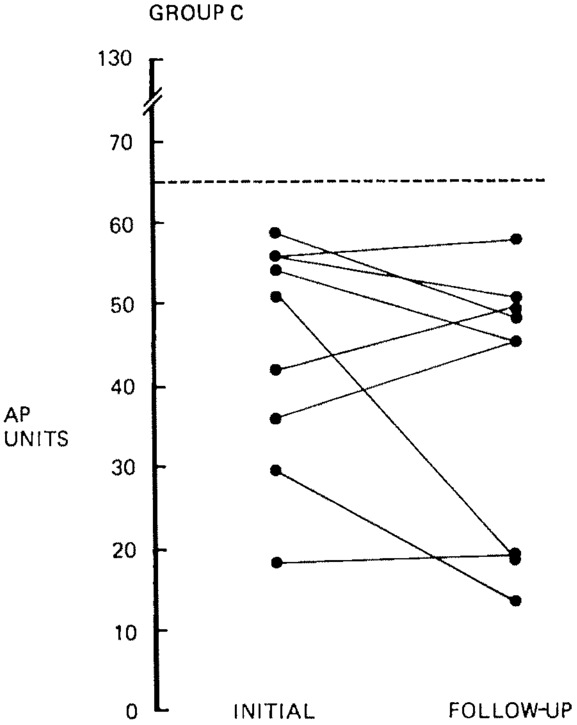

Fig. 3 Results of parenchymal transit times in patients who were renographically unobstructed at the time of presentation

have undergone serial studies; of the remaining 5 cases follow-up studies are awaited in 3, and 2 have refused further investigation.

Of the 6 cases in which follow-up studies were performed there was one in which a borderline renographic obstruction has persisted for one year; overall renal function in this patient, whose opposite kidney is poorly functioning, has deteriorated but there have been episodes of ascending urinary tract infection and it is difficult to know the cause of the functional impairment.

In the remaining 5 cases renographic evidence of persisting obstruction was found at follow-up studies performed between 3 and 12 months after the initial presentation. In 3 of these cases the contralateral kidney was normal and there was no change in overall or differential renal function during the period of follow-up. In one case the raised PTT was found in the presence of normal whole kidney isotope transit time and the radiological dilatation and the increased PTT were thought to be due to reflux nephropathy and renal ischaemia.

The remaining case was an elderly patient who had a solitary kidney and a neuropathic bladder. Renal function deteriorated but surgery was not undertaken because it was considered that the likelihood of a successful ureteric reimplantation was not sufficiently good to warrant operative intervention.

Group C (Fig. 3)

Twenty-five patients presented with ureteric dilatation in whom initial gamma camera studies showed no evidence of obstruction. There were 9 cases in which follow-up studies were clinically indicated: ureteric stones were the cause of persisting ureteric dilatation in 3 of these cases and conservative treatment was justified on the grounds of the absence of symptoms and normal gamma camera studies. The causes of persisting ureteric dilatation in the remaining 6 patients, 3 of whom had impaired function in the contralateral kidney, were congenital megaureter (2), post-operative fibrosis (1), retroperitoneal fibrosis (1), radiotherapy (1) and suspected ureteroileal stenosis (1). In no case was there any deterioration in overall or differential renal function.

Group D

There were 5 cases who were renographically equivocal. In all of these patients there was marked impairment of renal function and in 4 cases no reliable figure for PTT could be given for that reason; in one case, because of an enormous hydronephrosis, it was not possible to define a region of interest over the parenchyma with sufficient accuracy.

Group E

Two patients who were initially obstructed renographically in whom differential function on the affected side was less than 10% of overall function underwent nephroureterectomy and one patient who was initially obstructed after radiotherapy for a carcinoma of the cervix (whose opposite kidney was in group D) died before follow-up studies had been performed.

A comparison was made between the diagnosis arrived at after clinical, radiological and biochemical data had been considered—the clinical diagnosis—with the results of the gamma camera studies (Table 3). In 24 cases the clinical and renographic diagnoses agreed that obstruction was present and in 15 cases there was no obstruction clinically or renographically. Of the 11 cases clinically equivocal the gamma camera study showed evidence of obstruction in 6 and no evi-

Table 3 Comparison Between the Clinical and Gamma Camera Diagnoses

		Clinical diagnosis		
		Obstructed	*Unobstructed*	*Equivocal*
Gamma camera diagnosis	Obstructed	24	0	0
	Unobstructed	5	15	5
	Equivocal	5	0	0

dence of obstruction in 5. Five cases which were renographically equivocal for the reasons described above were all thought to be obstructed on clinical grounds.

Discussion

In an earlier study (Whitfield *et al.*, 1978) we showed that when PTT was greater than 72 Ap units, a significant degree of pelviureteric junction obstruction was present. In this study we have lowered the upper limit of normal PTT to 65 Ap units since we believe that the increased capacitance of the upper urinary tract reduces the pressure gradient from the glomerulus to the site of ureteric obstruction, producing a graded response of salt and water reabsorption in response to raised intratubular pressure.

We recognise that renal ischaemia may cause an elevated PTT but in the clinical context and in the presence of a normal whole kidney, tracer transit time confusion is unlikely to occur, though difficulty might arise if a degree of obstruction co-existed in a kidney in which there was a significant degree of ischaemic damage.

The rate of recovery of PTT following the relief of obstruction varies, depending partly upon the initial level of PTT but more upon the length of time for which the obstruction has been present. At the present time we are unable to predict the potential for recovery of renal function on the basis of PTT levels, but it is evident that alterations in PTT are a much more sensitive indication of the presence of obstruction than changes in percentage differential renal function. There was, in this series, poor correlation between the degree of ureteric dilatation seen radiologically and the presence or severity of obstruction as judged by the gamma camera study.

We believe that deconvolution analysis of the gamma camera renogram is a safe, reliable, non-invasive method of diagnosing ureteric obstruction. It provides the best method currently available for monitoring the effects of acute or chronic obstruction on renal function and enables the clinician to plan management on the basis of accurate information on nephron function.

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The Prognostic Value of Probe Renography in Ureteric Stone Obstruction

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Summary—During a 4-year period 143 ureteric stone patients were monitored with probe renography during and after obstruction. Cases with obstruction of short duration (less than 2 weeks) all did well. In cases with longer duration the renographic function values could be used to predict irreversible kidney damage. Stone size showed no correlation with functional impairment. Infection proximal to ureteric stones accelerated kidney damage.

Recommendations for the control of ureteric stone patients are given.

For decades urinary tract obstruction has been known to cause kidney damage and the duration of obstruction as well as infection have been recognised as important factors in this process.

Until the introduction of isotope renography (Taplin *et al.*, 1956) unilateral variations in kidney function were impossible to measure in clinical work. Since then, however, renograms have gained a place as one of the most important tools in the diagnosis and follow-up of upper urinary tract obstruction (Britton and Brown, 1971; Mogensen *et al.*, 1976; O'Reilly *et al.*, 1979). Experimental work (Katul and Wax, 1968) has shown the correlation between duration of obstruction and renographic uptake phase, but little clinical work has been presented on the subject. Having used probe renograms extensively in patients with ureteric stones, we find it valuable to report our results.

Material and Methods

The data on 239 patients admitted from January 1976 until July 1980 with verified unilateral ureteric stones were reviewed. In 96 cases renography had not been performed during obstruction because of immediate stone passage or clinical indication for operation, but in 143 patients there was sufficient renographic data to compare obstructive and post-obstructive values. The primary choice in all patients was ^{131}I-hippuran probe renography with electronically assisted kidney location (Jensen *et al.*, 1977) and only in very few cases was an additional gamma camera investigation needed to diagnose ectopic or non-functioning kidneys. Relative kidney function was estimated as the percentage of isotope uptake at 2 min with normal values 43 to 57%. Figure 1 shows the age and sex distribution, which correlates well with other published results (Sandegaard, 1956; Marshall *et al.*, 1975). Forty-five cases were recurrences, but apart from the slightly higher mean age the 2 groups did not differ significantly and they have been analysed as one.

Results

In 69 patients function was not impaired during

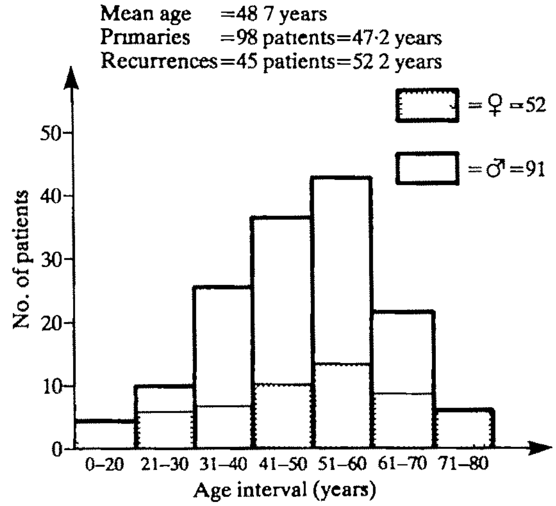

Fig. 1 Age and sex distribution.

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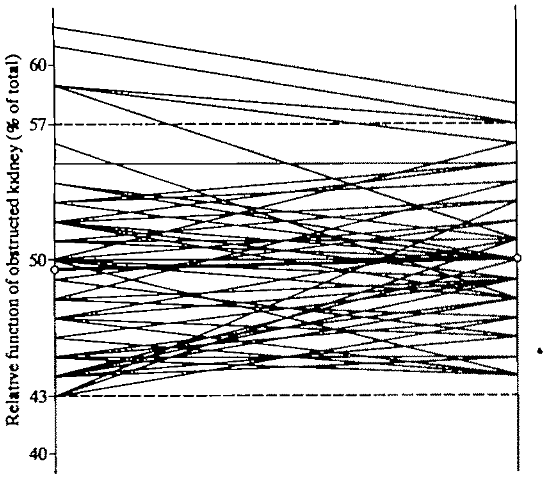

Fig. 2 Change in function in patients with initially normal function. Obstructive *v.* post-obstructive values (o——o = mean).

obstruction and irrespective of the time from onset to stone passage (up to 3 years) all remained normal when obstruction was relieved (Fig. 2). The mean values are almost exactly at the 50% level.

In 74 patients function was impaired during obstruction and their obstructive and post-obstructive values are shown in Figure 3. According to the duration of obstruction they have been separated into groups of less than 2 weeks, 2 to 4 weeks and more than 4 weeks. All cases in the short duration group returned to normal, whereas 3 out of 17 in the 2 to 4 weeks group and 11 out of 31 in the long duration group had irreversible kidney damage. The differences were not significant between the first 2 groups but highly significant ($P<0.01$) between the first and third group (Mann-Whitney test). In all 3 groups there was a significant improvement in function after stone passage.

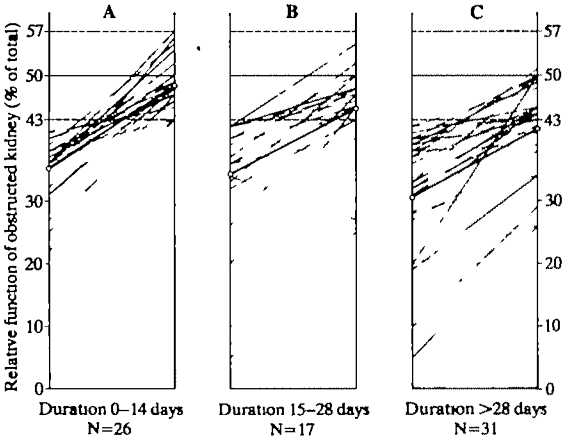

Fig. 3 Change in function in patients with initially impaired function. Obstructive *v.* post-operative values with correlation to duration of obstruction (o——o = mean).

Stone size and function during obstruction are compared in Table 1. Small and medium size stones caused similar degrees of obstruction and the trend towards more severe functional impairment with big stones is insignificant.

Table 2 correlates stone size and incidence of spontaneous passage, underlining the finding of other authors that stones bigger than 6 mm rarely pass spontaneously. Quite a large proportion of very small stones have been treated operatively in this series, and the table demonstrates our policy of intervening surgically when patients have functional impairment.

The pyelographic changes during obstruction are compared with renograms in Table 3. It is obvious that in the severely hydronephrotic kidneys function is decreased, but with moderate hydronephrosis pyelography does not give information about function and even in cases with slight dilatation there may be impaired function. In Table 3, however, a delayed nephrogram phase and the retention of contrast in the upper urinary tract have not been considered and such factors certainly increase the value of intravenous urography in the assessment of kidney function.

The influence of age on kidney recoverability is illustrated in Table 4. The numbers are small and though the young age groups seem to do somewhat better, the difference is insignificant. An important source of error in this table is the well known fact that young patients with functional impairment are subjected to more active treatment than the elderly.

In the cases with decreased function, infection proximal to the stone seems to accelerate kidney damage. We treated 6 such cases, most referred to the department with septicaemia, and the functional results are shown in Figure 4. Only when decompression of the upper tract was performed within a few days did the kidney recover and total

Table 1 Correlation Between Stone Size (Smallest Diameter) and Functional State of Obstructed Kidney

	Normal function	*Impaired function*	
<3 mm	13	13	A
3-6 mm	49	46	B
>6 mm	6	16	C

Table 2 Correlation Between Duration of Obstruction, Stone Size and Treatment

	Spontaneous passage			*Operative treatment*		
	<3 mm	3-6 mm	>6 mm	<3 mm	3-6 mm	>6 mm
0-14 days	7	6	0	5	12	3
15-28 days	6	5	0	0	11	2
>28 days	6	31	1	2	29	17

Table 3 Correlation Between Degree of Hydronephrosis and Functional State of Obstructed Kidney

	Normal function	*Impaired function*
No hydronephrosis	12	4
Moderate hydronephrosis	53	51
Severe hydronephrosis (or no uptake)	1	21

destruction or severe loss of function resulted when infection lasted more than 2 weeks.

Discussion

For some years there has been a tendency to refine renography using gamma cameras exclusively and even computing the results using advanced mathematics (Britton and Brown, 1971). Though we consider transit-time estimation a valuable new method, we have found it difficult to apply in cases with no excretion during the period of investigation. We find probe renography a sufficient and valuable tool for most cases of upper tract obstruction and still use this method for the vast majority, though obviously the fluctuations in obstruction are a source of error when ureteric stone patients are studied as a model of upper tract obstruction. Taking the number of patients studied into consideration, however, we find it reasonable to conclude that the figures support experiments by Katul and Wax (1968) in predicting irreversible kidney damage if obstruction lasts longer than 2 weeks and if the renogram during this period shows impaired function. Furthermore, we conclude that in patients with large stones (more than 6 mm), spontaneous passage is unlikely and operation should not be postponed. Small stones tend to pass spontaneously but a significant number impair function, which may warrant surgical intervention, and renograms should be performed even in these cases.

Infection proximal to ureteric obstruction causes a bad prognosis for the kidney and we treat these cases as emergencies, by passing a tube antegradely or retrogradely or by removing the stone as the primary procedure.

The schedule that we use for the diagnosis and follow-up in ureteric stone patients is shown in Figure 5. It may be argued that since few cases of terminal renal failure are caused by ureteric stone obstruction, conservative approach is reasonable, but as surgical treatment of ureteric stones carries a very low morbidity rate and as post-obstructive kidney damage may lead to elevated blood pressure we find our strategy well justified.

Table 4

	Impaired function	
	During obstruction	*After release*
≤50 years	34	3
>50 years	38	11

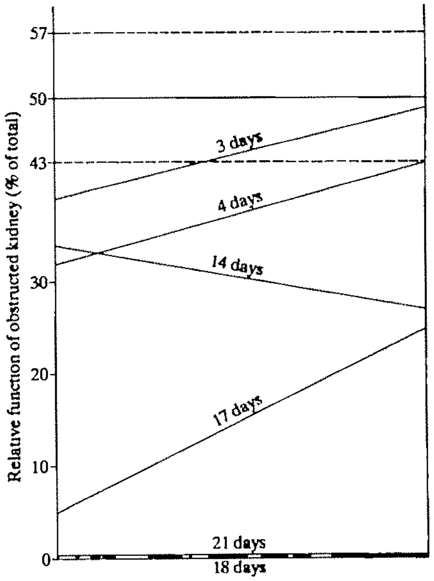

Fig. 4 Change in function in patients with impaired function and infection during obstruction. Duration of infection stated.

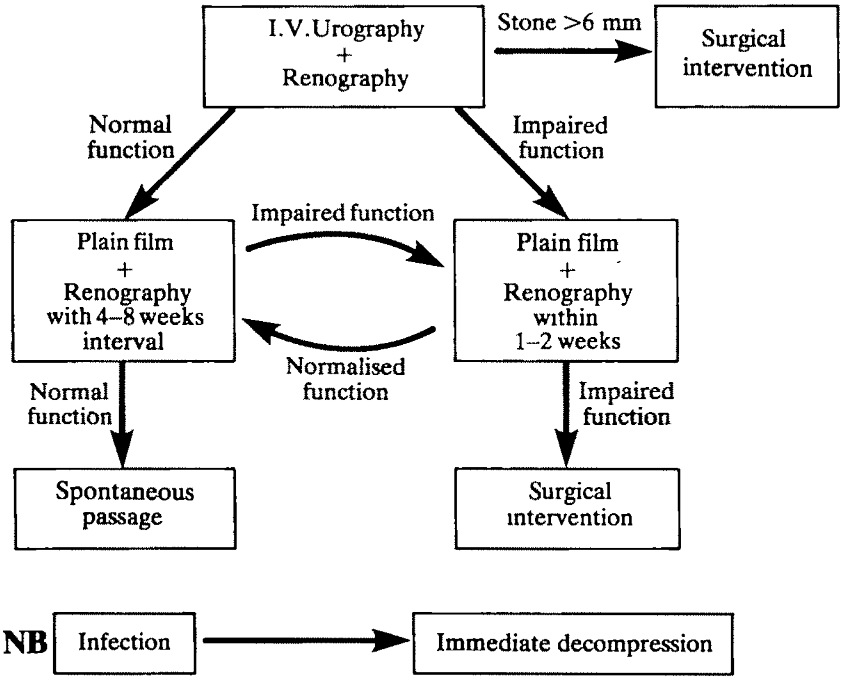

Fig. 5 Proposed follow-up of ureteric stone patients.

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Regional Renography in Segmental Renal Disease

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Summary—Twenty-nine patients with symptomatic segmental renal disorders were studied by regional renography. Twenty-three patients had duplex kidneys and 6 had other segmental disease. Abnormal gamma camera findings included ureteroureteric reflux, vesicoureteric reflux, impaired function, obstruction and non-obstructive dilatation. Comparison between renography and radiology in duplex kidneys showed agreement in 10 cases. In 7 kidneys the gamma camera provided additional information and in 6 cases the X-rays alone were abnormal.

It is concluded that regional renography should be performed wherever possible to complement conventional radiology in the functional and urodynamic evaluation of segmental renal disease.

In recent years improvements in nuclear medicine instrumentation and the provision of suitable radiopharmaceuticals have permitted the accurate definition of different areas within the same kidney. It has therefore been possible to assess functional and urodynamic abnormalities in individual segments of diseased kidneys. This report describes the clinical application of regional renography in the evaluation of patients whose symptoms were possibly due to segmental renal disorders. The purposes of this study were to assess the contribution of gamma camera renography to the overall management of the patients and to compare the results of this test with those of standard radiology.

Patients and Methods

Twenty-nine kidneys were studied in 29 patients. These included 17 incomplete duplex kidneys, 6 with complete duplex systems and 6 with other segmental disorders. The latter miscellaneous group had pyelonephritis or stone disease demonstrated on urography and involving particularly a single pole of affected kidneys. The presenting symptoms are shown in Table 1. All of the patients had an initial intravenous urogram; in some instances, where indicated, micturating cystography and retrograde pyelography were subsequently carried out. The gamma camera studies were performed with patients in a normal state of hydration and there was no specific preparation. The patients were seated in front of the gamma camera and an intravenous injection of ^{123}I-Hippuran was given in a dose of 15 μCi/kg body weight. Images were stored in an on-line digital computer system at 20 s intervals for periods ranging from 20 to 40 min. If indicated for the determination of the presence or absence of obstruction in affected segments the test was combined with a diuretic stimulus, frusemide being given before or during the study (O'Reilly *et al.*, 1979).

On replaying the images early frames were summed for the identification of the whole kidney areas. Slightly later frames were used for the definition of different regions within the same kidney. It was found, for example, that the 2 moieties of duplex kidneys were often best separated from one another at approximately 8 to 10 min after the start of the test. The distinction between segments was made wherever possible

Table 1 Presenting Symptoms of Patients Studied

Loin pain	13
Urinary infection	8
Loin pain/urinary infection	4
Frequency	3
Nocturia	1

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 2 Incomplete Duplex Kidneys—Abnormal Gamma Camera Study

Gamma camera renogram		*X-ray*		*Management*	
Ureteroureteric reflux	5	Dilated upper tracts		Conservative pyelopyelostomy	 4
Vesicoureteric reflux	1	Negative micturating cystogram		Reimplantation	1
Delayed excretion	1	Hydronephrosis		Heminephroureterectomy	
Impaired function	3	Pyelonephritis Calculus	2 1	Conservative pyelolithotomy	

and, in most instances, with reference to the urogram findings. Areas of interest were flagged using a light pen over the whole kidneys, a background region, the bladder, individual segments of affected kidneys and where appropriate over the ureters. Activity time curves were determined for each of these areas. The relative function of both whole kidneys was calculated by measuring the uptake of the tracer in each renal area during the first few minutes of the test and correcting for background activity. The contribution of individual areas within the kidneys to the overall renal function was also estimated.

Results

Duplex Kidneys

The results of gamma camera renography together with radiological findings and patient management are shown in Tables 2 and 4.

Incomplete Duplex Kidneys

Abnormal gamma camera studies were found in 10 of 17 cases (Table 2). Five patients had ureteroureteric reflux demonstrated on regional renography. Four of these cases had ureteroureteric reflux of the "see-saw" or "yo-yo" variety; in the other case "up and down" ureteroureteric reflux was detected (see below). Figure 1 shows the derived regional renogram curves from a patient with marked ureteroureteric reflux in the right kidney associated with loin pain. A pyelopyelostomy was subsequently carried out and Figure 2 shows the regional renograms 12 months after the operation, at which time the patient was symptom-free. Apart from a slight delay in excretion from the lower moiety post-operatively there is no abnormality.

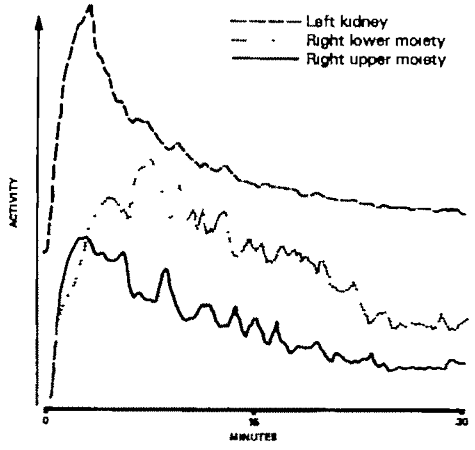

Fig. 1 "See-saw" reflux, right incomplete duplex kidney.

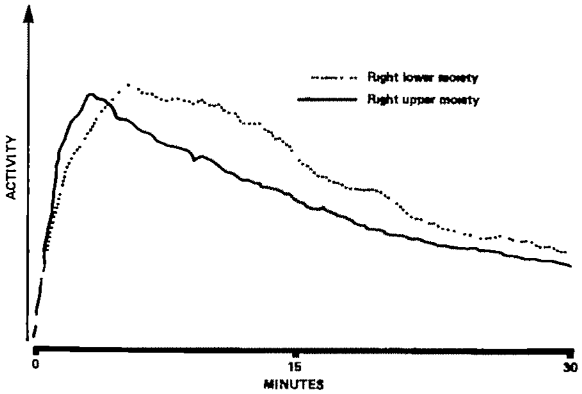

Fig. 2 Same patient as in Figure 1, 12 months after pyelopyelostomy.

The regional renogram curves from a patient with the "up and down" variety of ureteroureteric reflux are shown in Figure 3. Increases in activity over the upper moiety of this right kidney are matched by corresponding decreases over the ureteric confluence. There are no such variations over the lower moiety and, although not shown in the figure, neither are there any changes over the bladder. Urine is therefore refluxing between the upper moiety and the ureteric confluence. This represents one of the varieties of "up and down" ureteroureteric reflux (see below). With the one exception already referred to, the patients with ureteroureteric reflux in this series have been managed conservatively.

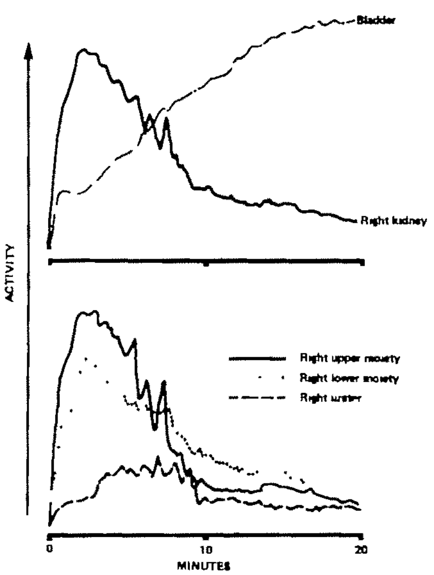

Fig. 3 "Up and down" ureteroureteric reflux, incomplete duplex kidney (urine refluxing between upper moiety and ureteric confluence).

Other abnormal findings on gamma camera renography were delayed excretion or impaired function. In one case with a stone in the lower moiety this area was found to be contributing only 14% of the overall renal function and a pyelolithotomy was performed. The radiological findings and management of the patients with normal gamma camera studies are shown in Table 3.

Table 3 Incomplete Duplex Kidneys—Normal Gamma Camera Study

X-ray		*Management*	
Stone	1	Nephropyelolithotomy	
Cortical loss	1	Conservative	
Clubbing/dilatation	3	Partial nephrectomy Conservative	1 2
Normal	2	Conservative	

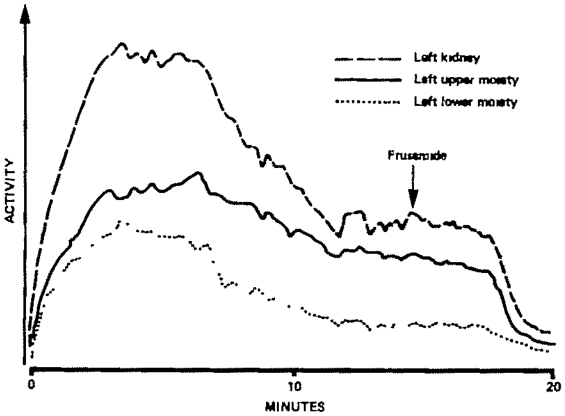

Fig. 4 Left complete duplex kidney: regional renograms showing non-obstructed left upper moiety.

Complete Duplex Kidneys

Abnormalities on regional renography were found in 3 of 6 cases (Table 4). Figure 4 illustrates the evaluation of a persistently dilated left upper moiety ureter following the excision of a ureterocele and reimplantation of both ureters. Regional renography with diuresis demonstrates that the ureteric dilatation is non-obstructive, the upper moiety draining satisfactorily after frusemide.

Other Segmental Disease

Five of 6 kidneys had abnormal gamma camera studies as shown in Table 5. An example of the use of regional renography in this group of patients is shown in Figure 5. Bilateral staghorn calculi were not well evaluated in both morphological and functional terms on standard urography. Gamma camera renography demonstrated poor tracer uptake in the right kidney, particularly at the right upper pole. Regional renograms derived by splitting the kidney into 2 halves confirmed the poor function in the right kidney, the upper pole being calculated as contributing only 2% of the global function. The patient eventually had bilateral renal surgery, including a right upper pole partial nephrectomy and nephropyelolithotomy.

Table 4 Complete Duplex Kidneys

Gamma camera renogram		*X-ray*		*Management*
Delayed excretion	2	V-U reflux Calculus	1 1	Conservative Pyelolithotomy
Delayed excretion (normal with diuresis)	1	Dilated ureter		Conservative
Normal	3	Normal V-U reflux	2 1	Conservative Antibiotics

Table 5 Miscellaneous Segmental Disease

Gamma camera renogram		*X-ray*		*Management*
Tracer retention	3	Pyelonephritis Stone	2 1	Conservative
Poor function	2	Stones/pyelonephritis Stone	1 1	Conservative Surgery
Normal	1	Upper tract dilatation	1	Conservative

Discussion

Segmental renal disorders provide an interesting and challenging facet of urological practice. Duplex kidneys, for example, are said to affect 6% of urological cases admitted to hospital and diseased moieties have been reported in 40% of these patients (Thompson and Amar, 1958). The commonest lesions have previously been found to be infection, hydronephrosis and nephrolithiasis and the commonest symptom associated with a duplex kidney is pain (Nation, 1944). Another observation concerning duplex kidneys is that reflux is more common than in single systems (Amar, 1968).

Radiological investigations of renal segmental disease provide a mainly anatomical assessment unless image intensification and video recordings are used. Prolonged periods of screening may be necessary to detect urodynamic disorders such as reflux, resulting in a high radiation dose. The value of radionuclide studies in the assessment of segmental disease has previously been appreciated (Constable and Joekes, 1972; Constable and Werry, 1972). The main advantages were cited as being early detection of minor disorders, functional comparison between moieties and the study of drainage abnormalities. More recently the use of radionuclides in the demonstration of uretero-ureteric reflux has been reported (O'Reilly *et al.*, 1978).

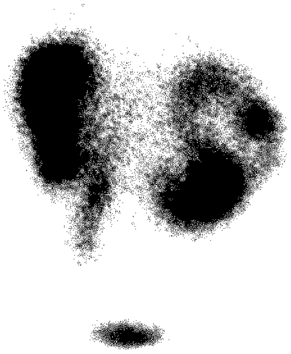

Fig. 5 Bilateral staghorn calculi. Gamma camera image (posterior view) at 15 to 20 min—poor tracer uptake right kidney, particularly at upper pole.

The increasing sophistication of nuclear medicine methodology and the potentially useful clinical information thereby gained have prompted the present study. Regional renography has been applied to a wide range of segmental disorders. The calculation of the relative contribution of a diseased segment to the overall function has been shown to aid a decision as to whether or not surgery would be beneficial. Such a measurement may also assist in devising a logical surgical approach; for example, significant impairment of function assessed quantitatively will indicate that a segment is not worth preserving.

The radionuclide evaluation of drainage abnormalities in individual segments has resulted in the demonstration of vesicoureteric and uretero-ureteric reflux. The investigation of the latter condition in patients with incomplete duplex kidneys and symptoms such as loin pain or urinary infection has been particularly interesting. Previous investigation of ureteroureteric or pyelopelvic reflux has involved either selective catheterisation of ureters, which is invasive, or image intensification, necessitating a high radiation dose. Tresidder *et al.* (1970) have observed that various forms of ureteroureteric reflux and pyelopelvic reflux can occur in incomplete duplex systems. The "see-saw" variety is well recognised. The "up and down" type may involve urine draining from one moiety into the other moiety (usually from the lower, more powerful pelvicaliceal system to the upper moiety) and then down the common stem.

Alternatively, urine may drain from one moiety to the ureteric confluence and then reflux back up to the same ureter. The patients in whom ureteroureteric reflux was demonstrated in the present series included 4 showing "see-saw" reflux and one with "up and down" reflux involving the *upper* moiety only. Radionuclide studies are therefore valuable in demonstrating not only the presence but also the type of uretero-ureteric reflux. These may be important observations since such reflux may be the cause of severe symptoms, particularly pain, and the appropriate surgery, such as side-to-side anastomosis of the ureters can be expected to be curative (Tresidder *et al.*, 1970).

The presence or absence of obstruction in individual renal segments can also be effectively studied by regional renography. The gamma camera has previously been described as useful in the diagnosis of superior infundibular obstruction and the assessment of stone disease causing obstruction (Constable and Joekes, 1972). The response of a segmental renogram to diuresis induced by frusemide has been informative in the present study. The example shown in Figure 4 demonstrates how the exclusion of obstruction in a dilated ureter helped to avoid unnecessary surgery.

The comparison between regional renography and radiological features in duplex kidneys has indicated that both methods of assessment agreed on abnormality in 6 cases and on normality in another 4 instances. The renogram provided additional information in 7 patients and the X-rays alone were abnormal in 6 cases. Regional renography therefore complements conventional radiology, each providing different but diagnostically useful information.

In conclusion, gamma camera studies are valuable in assisting the clinical management of segmental renal disease. The most important applications are in the investigation of duplex kidneys with particular reference to the determination of the functional contribution of individual segments, the diagnosis of ureteroureteric reflux and the assessment of obstruction.

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Part of this work was included in a thesis submitted by E. W. Lupton and approved by the University of London for the degree of MD.

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The Location of Urinary Calculi Using Radionuclide Imaging

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Summary—A method of *in vivo* labelling urinary calculi with ^{99m}Tc-methylene diphosphonate is described. This enables a radionuclide image of the stones to be produced and permits their location at operation by means of a small scintillation detector. The degree of uptake of the radiopharmaceutical on renal stones appears to depend on a number of factors, particularly the chemical composition of the stones.

It is often difficult to locate small stones and stone fragments during the operative removal of renal calculi. The purpose of this work was to determine whether stones could be labelled with a gamma ray emitting radionuclide and to see if this could aid in their location.

The radiopharmaceutical used for such a purpose must have certain characteristics.

1. It must be excreted by the kidneys in order to provide *in vivo* labelling of the calculi.
2. It must be readily bound to renal calculi.
3. The binding must be secure against leaching by normal urine flow.
4. The radionuclide used must emit radiation which can be readily detected by conventional equipment.
5. The physical and chemical properties of the compound should be such as to minimise radiation dose and toxicity.

A number of compounds labelled with the radionuclide Technetium (^{99m}Tc) were evaluated in a series of *in vitro* experiments and it appeared that ^{99m}Tc-methylene diphosphonate (MDP) best satisfied the above criteria. Given the similarity between the growth of bones and renal stones it is perhaps not surprising that this agent, which is widely used in skeletal imaging, should appear so promising. It was therefore decided to carry out a series of *in vivo* measurements on selected patients using MDP.

Patients and Methods

Twenty patients were studied in this preliminary series, each of whom gave their informed consent to the procedures involved. Twelve patients had surgery for removal of stones; one declined surgery, one had a papillary carcinoma of the renal pelvis and one had sloughed renal papillae. Three patients who had had bone scans were included in the series as controls, as were 2 patients who were subsequently found to have passed their stones before imaging.

Each patient was injected with 15 mCi (0.5 GBq) of ^{99m}Tc-methylene diphosphonate (Amersham International Ltd). No prior preparation was used.

Imaging was performed 24 h after injection using a large field view gamma scintillation camera (Elscint Ltd—Dymax LF). Anterior and posterior views, including kidneys, ureters and bladder, were routinely collected as 10-min exposures and stored as 64 × 64 matrices on an on-line computer (Digital Equipment Corporation—PDP11/40—Gamma-11 system). Each radionuclide image (Lithogram) was corrected for camera non-uniformity. The posterior view was found to be best for renal pelvic and upper ureteric stones, the anterior view for lower ureteric stones (Fig.).

In the last 6 subjects, a small sodium iodide detector, coupled to a photomultiplier by means of a flexible light guide, was used to locate labelled stones in the exposed kidney. A similar device has been described by Harvey and Lancaster (1981) for locating areas of increased bone uptake of ^{99m}Tc-MDP.

The calculi or fragments removed at operation

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

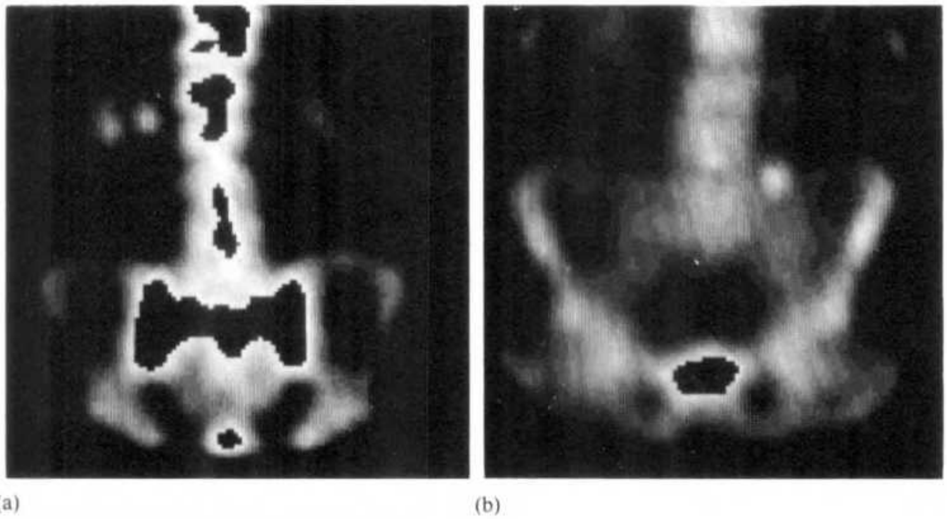
(a) (b)

Fig. Radionuclide lithograms: (a) Posterior; (b) Anterior.

were washed in saline and counted in a sodium iodide well-counter. The radionuclide uptake of individual stones was expressed as a ratio of the activity administered to the patient. In 7 subjects a section of rib, removed as part of normal surgical procedures, was assayed in the same way.

Results

The Table shows the results from the 12 patients who had stones removed. Small stones and fragments were assayed individually but when several stones or fragments were removed from one patient the activities have been added together. Where a large staghorn was removed, its activity has not been included because of the problems involved in estimating the non-uniformly distributed activity on the surface of such stones.

The radionuclide lithograms were rated as positive (2), equivocal (1) or negative (0) by visual inspection. A positive example is shown in Figure 1, together with the removed stones. The images obtained from the 5 control subjects were all negative, as were those from the patient with papillary carcinoma of the renal pelvis. The patient with sloughed papillae showed areas of increased uptake in the renal pelvis and ureters. Three patients (E, G and I) with proven stones had negative lithograms. No false positives have been obtained. The results of the chemical analysis of the stones are included.

Table Uptake of ^{99m}Tc-MDP on Renal Calculi

Subject	*Number of small stones or fragments assayed*	*Total weight of assayed stones (grams)*	*Total uptake (% administered dose)*	*Scan 2 + ve 1 equivocal 0 − ve*	*Chemical composition*		
					Calcium oxalate	*Magn. ammon. phosph.*	*Calcium phosph.*
A	3	0.27	0.21	2	1.4	3.0	82
B	1	0.20	0.072	2	29	0	41
C	1	0.24	0.023	1	45	0	42
D	4 (S)	0.62	0.29	2	1.0	51	32
E*	1	1.51	0.014	0	84	0	4.3
F	1	0.68	0.21	2	—	—	—
G*	1	0.95	0.020	0	79	0	11
H	4 (S)	5.42	0.16	2	0.2	28	52
I*	1 (S)	0.19	0.010	0	80	0	0
J	3 (S)	1.83	0.35	2	71	3.9	7.3
K	2	0.67	0.064	1	2.4	4.7	72
L	7 (S)	5.61	0.23	2	0	49	34

(S) Large staghorn calculus removed but not assayed.

The mean uptake of the 7 removed rib sections, which were of comparable size (mean weight 1.15 g), was 0.0068% of administered dose (range 0.0036-0.012%).

The portable probe used in monitoring the exposed kidney at operation revealed the presence of stone fragments, giving readings which correlated with the location of the fragments. Stones of dimension 2 to 3 mm have been detected with both scan and probe.

Discussion

^{99m}Tc-MDP is currently the agent of choice in radionuclide imaging of bone (Subramanian *et al.*, 1973). The presence of activity in the urinary tract on many bone scans, usually performed 2 to 4 h after injection, confirms that MDP is excreted by the kidneys (Hattner *et al.*, 1974). There is also evidence that it is taken up by non-skeletal calcified tissue (Rosental *et al.*, 1977; Casara *et al.*, 1979). This report has demonstrated that it is also bound to urinary calculi and if administered intravenously this labelling can be effected *in vivo*.

The results (Table) show a clear correlation between radionuclide uptake and lithogram finding and a marked correlation between uptake and composition. Stones which are predominantly phosphate show a much higher uptake than those composed largely of oxalate. Reduced uptake and poor visualisation were observed in 3 subjects (E, G and I), all of whom had oxalate stones. Renal function may influence uptake but it has not been possible to assess its contribution in this series. One patient, not included in the series, was found to have a cystine stone which was not revealed by imaging because uptake was low (0.003% of administered dose).

Each of the 3 control subjects who had bone scans performed showed MDP in the renal pelvis after 2 h, but none at 24 h. Thus urinary MDP is unlikely to produce artefacts in the lithogram or in the probe measurements. This has been confirmed by counting samples of urine obtained at operation. The 2 patients who had passed stones also showed no abnormality. Skeletal uptake is still present at 24 h, but it is normally much less than stone uptake. Unless the stone is situated close to the spine, this does not present a problem. The principal contribution to unwanted background appears to be blood activity, particularly in probe measurements.

The technique appears to differentiate between papillary carcinoma of the renal pelvis and sloughed papillae occupying the pelvis or ureters, which both appear as non-opaque filling defects on conventional radiographs.

The portable, flexible probe appears to be helpful in locating stone fragments in the exposed kidney. Current developments are aimed at increasing sensitivity and spatial resolution.

The radiation dose to the patient is the same as for a conventional radionuclide bone scan and that to theatre staff has been shown to be within permissible limits.

Conclusion

It has been demonstrated that urinary calculi can be labelled with ^{99m}Tc-MDP to a degree that enables them to be imaged and detected by conventional means. This has helped in locating stones at operation. The technique may have a role in the differentiation of non-opaque filling defects in the urinary tract.

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In Vitro Studies on Optimum Preparation of Coagulum for Surgery of Renal Calculi

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Summary—In renal calculus surgery, human dried fibrinogen produces a coagulum with a much greater tensile strength, stickiness, deformability and extractability than cryoprecipitate, which produces a relatively weak and friable clot. A useful coagulum may be prepared at room temperature at any convenient time prior to use if a mixture of 19 ml human dried fibrinogen solution and 1 ml thrombin solution is used. If mixed in a single syringe and injected within 35 s through a butterfly needle into the renal pelvis, complete mixing of the solutions is guaranteed.

By using this simple method, the unpredictability of the coagulum can now be eliminated and a strong and elastic clot can be produced.

Since the introduction of the use of a fibrin clot made by adding thrombin to fibrinogen in pyelolithotomy (Dees and Fox, 1943; Dees, 1946 and 1955), several different ways of forming coagulum have been advocated, although little work has been done to justify many of them. Recent authors have suggested that cryoprecipitate may be as effective as human dried fibrinogen (Rathore and Harrison, 1976; Fischer, 1978; Marshall, 1978) and offers less risk of transmitting the hepatitis virus (Rathore and Harrison, 1976), but is the resulting coagulum strong and reliable in practice? Coagulum pyelolithotomy has a poor reputation because it has been difficult to make a useful, strong and reproducible coagulum in ordinary operating room conditions.

We set out to find the optimum conditions for preparing a coagulum that met the needs of the surgeon faced with multiple or friable calculi. Marshall (1978) measured the tensile strength and found it was proportional to the concentration of fibrinogen in the mix and inversely proportional to the concentration of thrombin (above a critical minimum). In practice, however, the surgeon also needs other qualities: *stickiness* to allow the clot to adhere to the fragments of calculus, *deformability* to allow the clot and the stone to be extracted through the neck of the calix, and *extractability* to allow the surgeon to seize the clot with forceps and pull, knowing that it will stretch but not break away.

We have attempted to evaluate these qualities by direct measurement in a simple *in vitro* system.

Materials and Methods

(1) Human dried fibrinogen (produced by the Lister Institute, Elstree) contains 2.2 g fibrinogen per bottle. This was reconstituted with 50 ml sterile distilled water, giving a fixed concentration of 4.4 g per 100 ml. Lesser volumes of water would not dissolve the fibrinogen effectively.
(2) Topical bovine thrombin (produced by Parke-Davis) contains 5000 units of thrombin. This was reconstituted with 100 ml sterile normal saline, producing a fixed concentration of 50 units per ml.
(3) Cryoprecipitate (produced by Brentwood Transfusion Centre) contains approximately twice the concentration of fibrinogen in plasma, ranging from 204 mg per 100 ml to 540 mg per 100 ml, the mean concentration being 400 mg per 100 ml.

The apparatus used for this study consisted of a conical flask (simulating the shape of a calix) fixed in a water-bath at a constant temperature of 37°C (Fig. 1). A non-stretchable cord (UK radio-spares flax-drive cord 50.976.5.) was suspended in the flask. The end of the cord was formed into a knot with 20 throws (measuring 0.8 cm/0.8 cm/0.8 cm). Both knot and flask were carefully cleaned and dried after each measurement to

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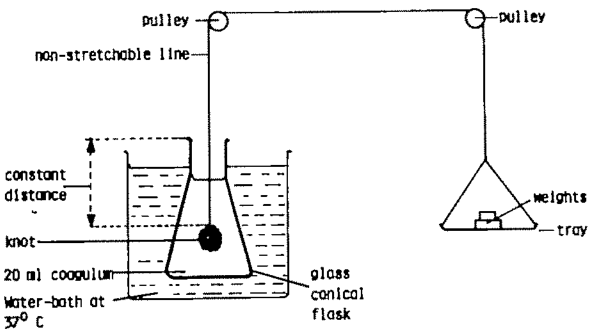

Fig. 1 Diagram of the apparatus used in the study.

keep'their properties constant. Two small pulleys and a tray for weights completed the apparatus.

The solutions of human dried fibrinogen and thrombin were drawn up in separate syringes and injected through a 19 gauge needle simultaneously into the flask in which the knot was suspended at a constant depth, to give a final volume of 20 ml.

The solutions were kept at varying temperatures (4°C room temp and 37°C) for varying times (30, 60 and 90 min) before being added to the flask. A drop of methylene blue was added to the thrombin.

Cryoprecipitate was thawed at 37°C for 5, 10 and 15 min before being used.

The time for the coagulum to form was studied at intervals of 3, 6 and 9 min. At the end of the set time, weights were gently added to the tray. We recorded (*a*) the weight required to pull the knot out of the coagulum (the pull-out weight). The mean of 3 results was plotted against the concentration of fibrinogen and thrombin, the temperature and age of the coagulum; (*b*) the deformability and extractability, *i.e.* the ease with which the clot could be removed from the flask with forceps: this was noted on a 3-point scale.

In the final 20 ml mixture, volumes ranged from 3:17 fibrinogen:thrombin to 19:1 fibrinogen: thrombin, *i.e.* (132 mg fibrinogen:850 units thrombin, to 836 mg fibrinogen:50 units thrombin). Ratios of cryoprecipitate to thrombin ranged from 8:12 to 19.5:0.5.

The effects of adding 1 and 20 mg calcium chloride to the mixtures were also assessed.

Results

(a) Concentration of fibrinogen The greater the concentration of fibrinogen in the final 20 ml mixture, the greater the weight required to pull the knot from the coagulum (Fig. 2). As the concentration of fibrinogen in the mixture increased beyond 25 mg/ml, the stickiness of the coagulum also increased and, at the pull-out weight, it was the coagulum around the knot that broke, rather than the knot pulling free. Extractability and deformability were improved with increasing concentrations, 42 mg/ml giving excellent results for both of these qualities. To demonstrate the excellent stickiness of the coagulum at high concentrations of fibrinogen, stones of different shapes, sizes and surfaces were placed in the flask, the mixture was added, and after 5 min the coagulum with all of the stones was extracted from the conical flask.

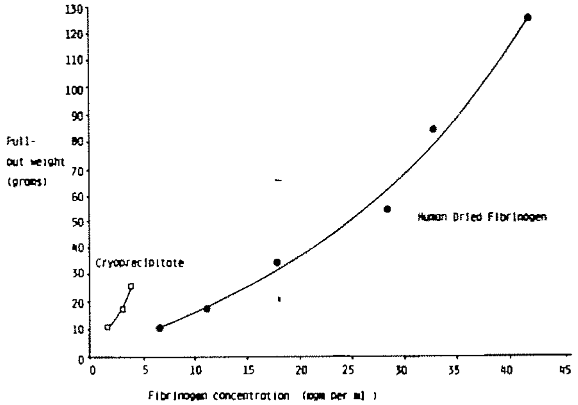

Fig. 2 Effect of fibrinogen content of coagulum on the pull-out weight.

Cryoprecipitate gave consistently poor results for both tensile strength and extractability even at its maximum concentration of 3.9 mg fibrinogen per ml final mixture and the maximum pull-out weight of human dried fibrinogen was nearly 5 times that of cryoprecipitate (Fig. 2).

(b) Concentration of thrombin With increasing concentrations of thrombin in the mixture the weaker the clot, and therefore less weight was required to pull the knot from the coagulum (Fig. 3). As the volume of thrombin decreased, the pull-out weight increased, but below the optimum level of 5% thrombin solution in the 20 ml mixture the pull-out weight fell. However, extractability was good with larger volumes of thrombin, although stickiness was poor because an incomplete coagulum had formed and free fluid lay between the flask and the coagulum, making extraction of the clot with forceps much easier, even though the clot was weak.

Pence *et al.* (1981) have recently suggested that pulmonary complications can arise from the use of coagulum in pyelolithotomy. However,

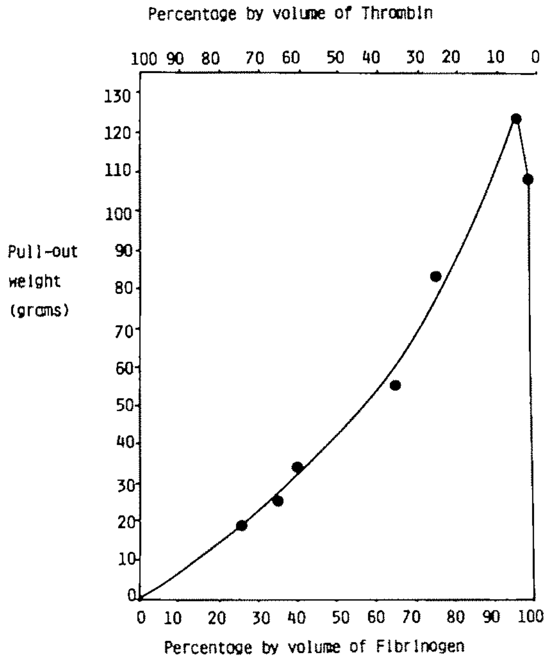

Fig. 3 Pull-out weight with varying volumes of human dried fibrinogen and thrombin solutions.

the volumes used in their study were far in excess of the volumes in this and other studies, and it is possible that the concentrations of thrombin they used were too great.

(c) Temperature The effect of temperature on the coagulum was small (Fig. 4), 37°C giving marginally better results. The length of time the prepared solutions remained at a given temperature before being added to the flask made no difference to the pull-out weight, stickiness or extractability.

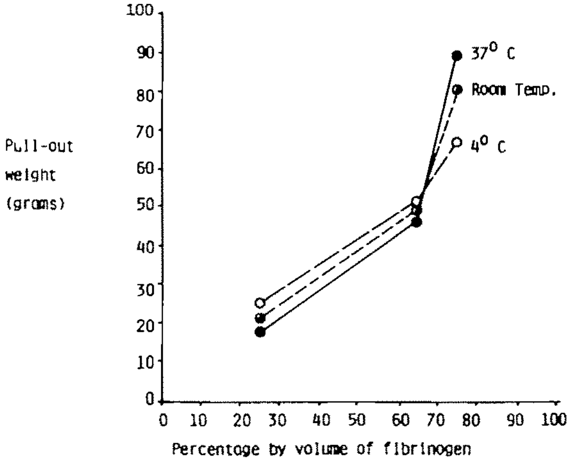

Fig. 4 Effect of temperature on the pull-out weight.

(d) Time Using volumes of thrombin in excess of 2 ml, clot formation was almost immediate, necessitating the use of separate syringes to introduce the thrombin and fibrinogen into the flask. By decreasing the volume of thrombin, clot formation was delayed, and at volumes of 1 ml thrombin to 19 ml fibrinogen solution, clot formation took approximately 38 s. Once clot formation had occurred, time was needed for the thrombin and fibrinogen to interact and form a firm fibrin clot. The pull-out weight at 3 min was consistently less than that at 6 or 9 min (Fig. 5), suggesting that more than 3 min should be allowed to elapse, after the introduction of the solutions, before extraction is attempted.

(e) Calcium The effect of adding 1 ml calcium chloride to cryoprecipitate was negligible (Fig. 6). (Solutions of 1 mg/ml and 20 mg/ml calcium chloride were used.) However, when added to the human dried fibrinogen solution it had a detrimental effect and the resulting clot became too brittle to be extracted from the flask in one piece, even though the pull-out weight and stickiness of the clot were increased.

(f) Methylene blue The addition of up to 5 drops of methylene blue had no effect on the resultant coagulum.

Discussion

The surgeon using coagulum requires a reliable and easily prepared formula. This study demonstrates that cryoprecipitate, as prepared by our

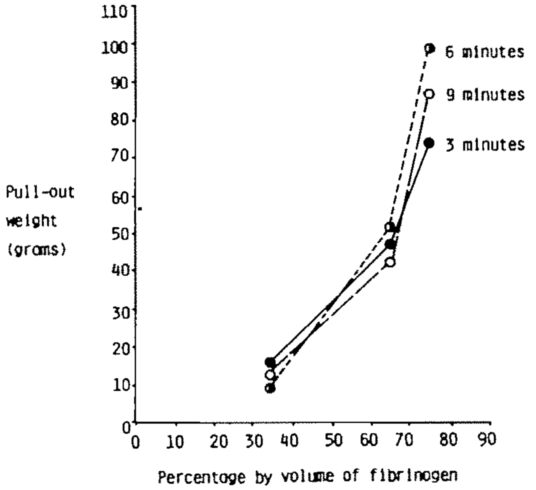

Fig. 5 Effect of age of coagulum at 37°C on the pull-out weight.

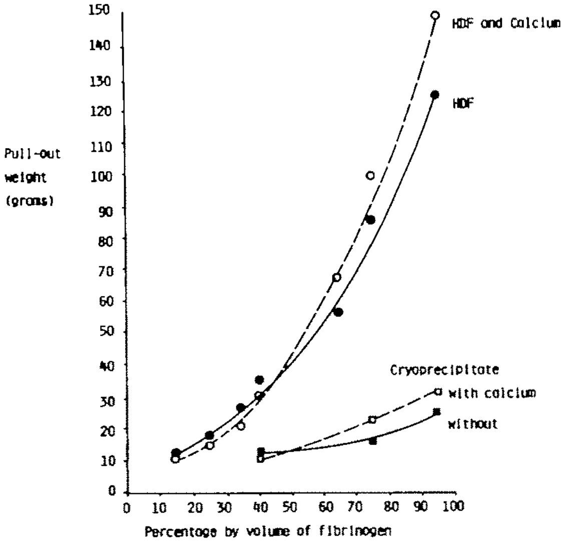

Fig. 6 Pull-out weight: effect of calcium on human dried fibrinogen and cryoprecipitate.

blood transfusion centre, cannot meet those requirements for 2 reasons: (*a*) cryoprecipitate contains insufficient fibrinogen (less than 10% that contained in human dried fibrinogen), and (*b*) the fibrinogen concentration varies in proportion to the amount of supernatant withdrawn at the time of preparation. This naturally leads to variations in the resulting coagulum.

Temperature is not a significant factor, nor is the time that the solution is kept at a specific temperature before mixing. Room temperature should be used and solutions prepared at any convenient time prior to use.

Using the suggested formula of 19 ml fibrinogen to 1 ml thrombin, clot formation occurs in approximately 38 s; the renal pelvis must be exposed and the 21 gauge butterfly needle with a 35 cm extension *in situ* before the thrombin is mixed with the fibrinogen in a single syringe.

There is no indication that calcium should be added to the mixture, but methylene blue can be added for clarity.

This study shows that:

(1) The tensile strength of coagulum is proportional to the concentration of fibrinogen and inversely proportional to the concentration of thrombin. Human dried fibrinogen achieves the best results.

(2) Excess thrombin weakens the clot and speeds its formation.

(3) Temperature is not critical and room temperature can be used.

(4) Contrary to previous reports, calcium is not required and may in fact be detrimental.

(5) Cryoprecipitate produces a friable and inelastic coagulum that is much less useful than coagulum formed from human dried fibrinogen.

(6) The time allowed for clot maturity, after introduction of the mixture, need be no more than 4 min.

A useful recipe has been found in practice to consist of 19 ml human dried fibrinogen solution, 1 ml thrombin solution and 1 to 3 drops of methylene blue.

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The Place of Extended Pyelolithotomy (Gil-Vernet Operation) in the Management of Renal Staghorn Calculi

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Summary—In the 17 years up to 1979 189 kidneys have had an extended pyelolithotomy for staghorn calculus and have been followed up. In only 1 of 96 unilateral cases did a stone form in a normal contralateral kidney, whatever the outcome of surgery on the affected side. Seven early nephrectomies were performed for non-function and in 6 bilateral cases, with advanced renal failure, surgery did not arrest the loss of renal function. Regrowth of stone occurred in 43 cases (complete staghorns in 24). Regrowth did not occur in 18 of 20 incompletely cleared kidneys nor in 22 of 41 with persistent infection. Renal function was improved in 13 of 15 cases where it had not already deteriorated beyond a critical point.

It is concluded that unilateral staghorn stones may be treated in their own right, without fear of compromising a normal contralateral kidney; that regrowth of stones is not inevitable, even with incomplete clearance; and that renal function is usually improved by surgery.

Thanks to the development of safe and reliable techniques for the removal of staghorn stones from the kidney (Gil-Vernet, 1965), it is agreed that the hazard of leaving a stone is far greater than that of doing nothing. At the same time it is recognised that in many kidneys it may be impossible to remove every fragment of stone, however hard one tries, and that some stones recur.

In this report we set out to answer 3 questions:

1. Does preservation of a damaged and incompletely cleared kidney pose a threat to the normal contralateral kidney?
2. Do kidneys that are incompletely cleared inevitably have a recurrence?
3. Does the removal of a staghorn calculus improve renal function?

Patients and Methods

Between 1964 and 1979 269 staghorn stones in 226 patients were studied in this unit. Their details have been recorded prospectively on punch cards. The initial management is shown in Table 1. Unfortunately the follow-up is incomplete: many of the younger patients have moved away and are lost; others were referred from overseas. Adequate follow-up from 1 to 17 years is available on 189 kidneys and forms the basis of this report.

The extended pyelolithotomy technique that was used was based on that described by Gil-Vernet but has been modified and improved from time to time (Gil-Vernet, 1965; Blandy and Tresidder, 1967). The first step has always been to control the renal artery. The renal pelvis and necks of the calices are then dissected out through the renal sinus. In many cases the whole of the stone can then be removed by pyelotomy.

When mushroom extensions of the stone prevent them from being drawn through the neck of the calix, small nephrotomies are made (Gil-Vernet, 1965), commonly through areas of scarred parenchyma. This is usually a minor procedure and is regarded as an integral part of an extended pyelolithotomy. Since Wickham drew attention to the logic of making nephrotomies parallel with the segmental arteries, we have always taken care to make them radial (Wickham *et al.*, 1974; Sleight *et al.*, 1980).

Similarly, the technique of Hohenfellner for identifying the main segmental arteries at operation with the Doppler probe was used (Hohenfellner personal communication). Whenever possible occlusion of the main renal artery was

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Initial Management of 269 Cases of Renal Staghorn Calculus

	Primary treatment 1964-79
Nephrectomy	34 kidneys
No surgery	12 kidneys
Extended pyelolithotomy	223 kidneys
Total	269 kidneys in 226 patients

avoided, since no clamp was regarded as wholly atraumatic to the intima of the vessel, but when necessary the artery was clamped and the simple method of cooling recommended by Marshall and Blandy (1974) was used.

Finally, a simplified version of coagulum pyelolithotomy was used to catch small peripheral fragments of stone and to identify those calices that had been explored and those that had not (Patel, 1973; Norris *et al.*, 1981).

Only in exceptional cases was a nephrostomy left in, and even less often was Renacidin or solution G used in an attempt to dissolve small residual fragments, since the hazards of introducing infection were felt to be greater than those of leaving a tiny fragment behind.

Results

No patient died from the operation and no kidney required removal for secondary haemorrhage.

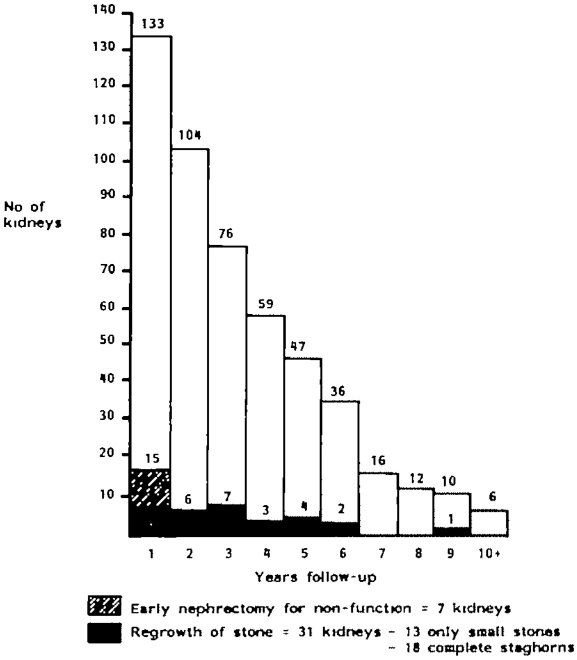

Fig. 1 Follow-up of infective renal staghorns.

Table 2 Extended Pyelolithotomy: Factors Affecting Recurrence

	Regrowth	*No regrowth*	*Total*
Incomplete clearance	2	18	20
Persistent infection	19	22	41

Effect on a Normal Contralateral Kidney

In 96 patients available for follow-up who initially presented with a unilateral staghorn stone, only one subsequently formed a stone in a normal contralateral kidney, regardless of the outcome of surgery on the affected side. This exceptional case was free of recurrence for 6 years and grew her second stone during pregnancy complicated by *Proteus* infection.

Recurrence After Removal

Even after a long follow-up in many cases, it is not possible to give an overall figure for the recurrence rate. Each year brings a small new risk of recurrence, so that continued follow-up is essential. We have studied the 3 main aetiological groups separately, since there is some evidence that they may behave differently (Bichler *et al.*, 1976; Wickham, 1976; Griffith, 1978).

1. Infective Calculi

The largest group had mixed magnesium ammonium phosphate stones with proven urinary infection (usually *Proteus mirabilis*). There were 145 kidneys in 125 patients available for follow-up. Six patients in renal failure continued to end-stage failure; the results from the remaining 133 kidneys

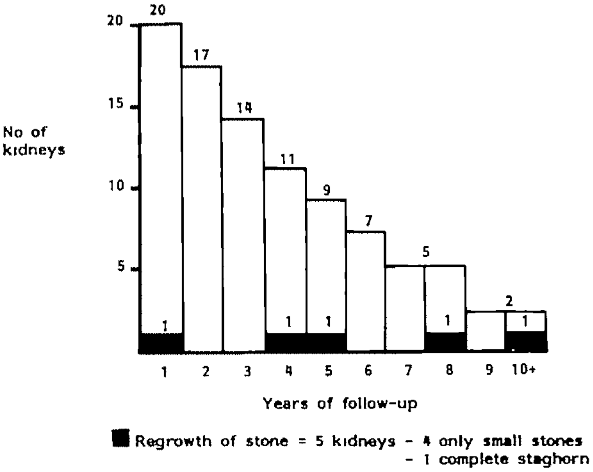

Fig. 2 Pure metabolic group: follow-up.

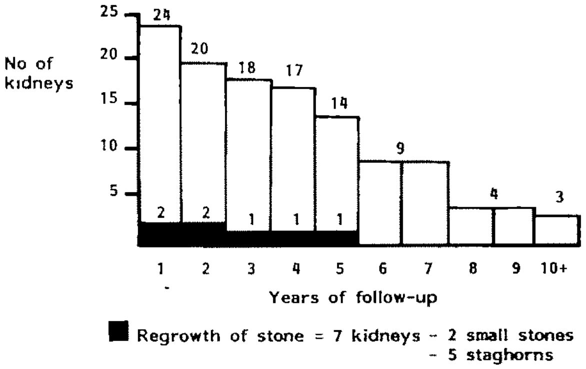

Fig. 3 Follow-up of staghorns with mixed infective and metabolic abnormality.

are shown in Figure 1. Ninety-five kidneys have remained clear and 6 of 8 that were re-done after a recurrent staghorn had formed also remain clear.

When residual fragments grew or new stones formed, it was often in the first year after operation and, indeed, half of the failures occurred within the first 3 years. Each year a small number of recurrences appeared, usually in a kidney that had been unchanged for several years. Two stones were precipitated by *Proteus* infection in pregnancy.

The causes of new stone formation were not always clear: although recurrences in this group commonly occurred in patients with persistent infection, 22 with persistent infection did *not* have a recurrence. Only 2 of 20 kidneys that were incompletely cleared regrew stones (Table 2).

2. *Metabolic Calculi*

Twenty kidneys with an obvious metabolic cause for their stones were followed up (Fig. 2). Two small stones recurred late (1 with cystinuria and 1 with primary hyperoxaluria); 15 remained clear during the period of the review.

3. *Stones of Mixed Aetiology*

The third group had a primary metabolic defect to which was added the effect of secondary infection (*Proteus* in at least half of them). This underlines the need for full metabolic investigation even when this organism is identified. When both aetiological factors are present, the outlook is worse (Fig. 3): 7 of 24 kidneys had recurrent stones, 2 of which subsequently went into renal failure.

Rate of Growth of Stones

As Broomfield pointed out over 200 years ago, stones can grow very fast given the right conditions and one may not be aware of them until they have destroyed the kidney (Broomfield, 1773). The speed of growth can seldom be measured with accuracy. In one ambulant patient without any previous evidence of stone disease, a struvite calculus appeared in 10 months in a radiologically normal kidney.

With recurrent struvite stones gradual regrowth over a number of years was seldom seen: the kidneys were usually quiet until some circumstances allowed rapid growth over a few months. Of 31 stones that regrew, 8 occurred within the first year and 21 within 3 years.

Effect of Surgery on Renal Function (Fig. 4)

Seven patients with unilateral stones came to early nephrectomy. All were infective in origin and the kidneys had very poor excretion on urography. They were not improved by surgery and should have been removed in the first place. Six infected patients were operated on in advanced renal failure (plasma urea over 40 mmol/l) and in none was the downward march halted, though it may have been slowed. Two patients with bilateral staghorns of mixed aetiology had recurrences and later died in chronic renal failure.

Where renal function was less severely impaired, the outcome was much better: 13 of 15 patients who were operated on with moderate elevation of plasma urea were improved. The 2 who were not improved had recurrence of stones.

Discussion

If extended pyelolithotomy were only a stepping

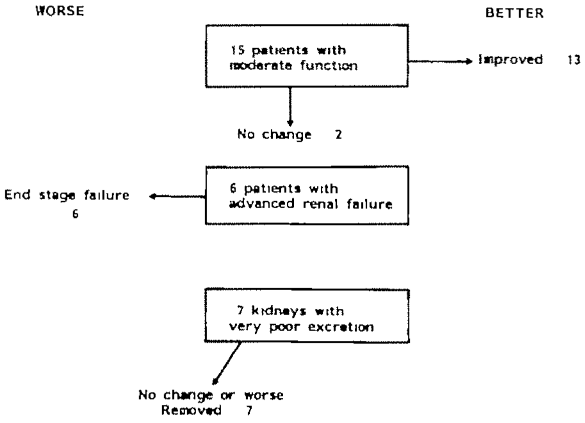
WORSE
BETTER
15 patients with moderate function
Improved 13
No change 2
End stage failure 6
6 patients with advanced renal failure
7 kidneys with very poor excretion
No change or worse
Removed 7

Fig. 4 Effect of surgery on renal function.

stone on the way to nephrectomy it would seldom be indicated, perhaps only when both kidneys were affected. We have shown that this is not the case: although there is a cumulative risk of recurrence year by year, regrowth is certainly not inevitable even when operation has failed to clear the kidney completely.

Recurrences tended to come early with the struvite stones and were more spread out with the others. With metabolic stones, removal cannot be a cure and the stone diathesis persists. Clearly only longer follow-up will show whether our apparently successful cases are really cured or whether we are seeing them in a relatively brief phase in a lifetime of stone formation. However, the results so far seem much better than those from pre-Gil-Vernet days (Williams, 1963).

A kidney with a staghorn stone may be treated in its own right. Failure to clear an affected kidney and persistence of infection, although unsatisfactory, do not compromise the normal kidney. Nonetheless, persistent infection, especially with *Proteus mirabilis*, needs the most thorough treatment.

As has been reported by others, extended pyelolithotomy usually improves impaired renal function and some patients may be saved from dialysis (Witherow and Wickham, 1980). In kidneys with very poor function, however, no improvement may be found and there would seem to be a critical point beyond which there is no point in trying to remove the stone.

The more extensive procedure of anatrophic nephrolithotomy appears to have no advantage over the Gil-Vernet operation. The results are similar (Boyce and Elkins, 1974); renal function is not improved, although deterioration is halted (Stubbs *et al.*, 1978) and the destruction of nephrons is greater (Fitzpatrick *et al.*, 1980).

These findings provide satisfactory answers to 3 possible criticisms of the extended pyelolithotomy. It is believed that this operation is the treatment of choice for the majority of renal staghorn calculi.

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Inosine in Ischaemic Renal Surgery: Long-term Follow-up

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Summary—Inosine, a purine nucleotide, has been used in 33 patients as a method of preventing ischaemic renal damage. The long-term results have been reviewed with a mean follow-up of 28 months.

Inosine was administered either intra-arterially or intravenously. Renal function was assessed by serum creatinine, creatinine clearance and divided function renography.

Inosine afforded satisfactory protection in ischaemic periods of up to 60 min, particularly if pre-operative function was normal. It was less reliable if pre-operative function was poor or in ischaemic periods greater than 60 min. Inosine is a helpful aid in ischaemic renal surgery.

Although renal function is adequately protected during periods of renal ischaemia by either surface or core cooling (Wickham *et al.*, 1974; Marberger *et al.*, 1978), the idea of administering a substance prior to ischaemia which would prevent renal damage and dispense with the extra equipment required for hypothermia is attractive. Many attempts to find such a substance have been made and inosine (Fernando *et al.*, 1976) and magnesium chloride—ATP (Lytton *et al.*, 1979) have been the most promising.

Inosine has been shown to prevent ischaemic renal damage when injected into the renal artery or into a peripheral vein (Wickham *et al.*, 1978, 1979). The purpose of this study was to review the patients who had received inosine and assess their renal function at late follow-up.

Patients and Methods

Thirty-three patients have received inosine (Trophicardyl, Laboratoire Chantereau, Arcueil, Paris) in order to prevent renal damage during a period of *in situ* renal ischaemia. Inosine was injected (30-60 mg/kg) into the renal artery immediately after clamping in 11 patients; it was injected into a peripheral vein 10 min before clamping of the renal artery in 22 patients. The only complication was an episode of paroxysmal arterial tachycardia in a patient already known to suffer from this condition.

Thirty-one patients had a nephrolithotomy (multiple radial incisions in 30, anatrophic incision in one); one patient had a local resection of a papillary transitional cell tumour of the renal pelvis and one patient had a partial nephrectomy. The ischaemic period ranged from 25 to 94 min (mean 52 min). In 23 patients ischaemia lasted for less than 60 min and in 10 patients it was greater than 60 min.

The age range was 18 to 67 years (mean 42 years). There were 14 male and 19 female patients. The follow-up was from 6 to 46 months (mean 28 months). Renal function was measured by serum creatinine, creatinine clearance, probe renography (^{131}I Hippuran), and gamma camera renography (^{123}I Tc-DTPA).

One patient had a previous history of urinary tuberculosis and one a previous history of acute tubular necrosis. Previous nephrolithotomy using regional hypothermia had been performed ipsilaterally in 6 patients and contralaterally in 7 patients. Multiple operations were performed in 2 patients. The contralateral kidney was absent or poorly functioning in 7 patients.

Results

Serum Creatinine (Figs. 1 and 2)

Pre-operative serum creatinine was normal (<0.13 mmol/l) in 24 patients and elevated in 9. In the

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

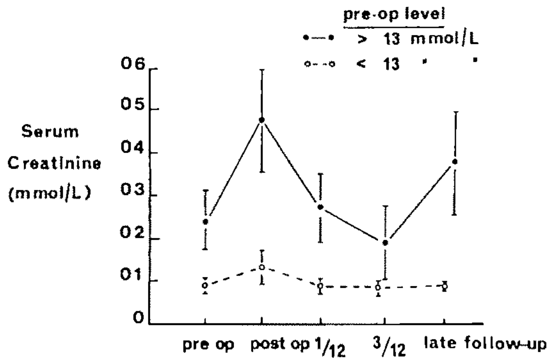

Fig. 1 Serum creatinine (mean ± SD) pre- and post-operatively in patients with normal and decreased function.

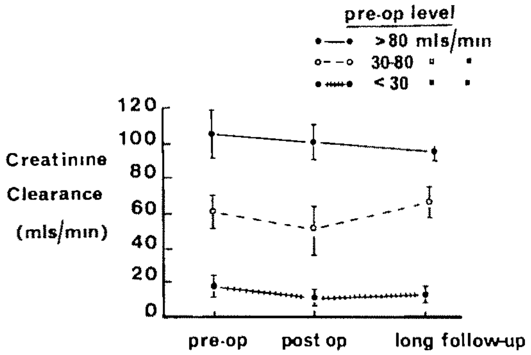

Fig. 3 Creatinine clearance (mean ± SD) pre- and post-operatively in patients with normal and decreased function.

patients with a normal pre-operative serum creatinine there was no elevation at any stage post-operatively or at late follow-up. The patients with elevated pre-operative serum creatinine (0.24± 0.07 mmol/l) had a rise to 0.47±0.12 mmol/l immediately post-operatively, but at 3 months it had returned to 0.19±0.08 mmol/l. At late follow-up the level had increased to 0.37±0.12 mmol/l. This increase was mainly due to 2 patients with worsening renal function because of chronic pyelonephritis. The serum creatinine was higher post-operatively if the ischaemic period was more than 60 min, but returned to normal levels by 3 months.

Creatinine Clearance (Figs. 3 and 4)

Fifteen patients had a normal creatinine clearance (>80 ml/min) pre-operatively. It remained normal at early and late follow-up. In the patients with a pre-operative creatinine clearance of 30-80 ml/min there was a decrease post-operatively, but this soon returned to pre-operative levels. In patients with poor pre-operative renal function, the level decreased from 17.3±4.0 to 9.3±3.3 ml/min at early follow-up and remained decreased at 11.3±4.0 ml/min at late follow-up.

When the ischaemic period was greater than 60 min, the clearance values decreased from a mean of 58.7 ml/min to a mean of 23.2 ml/min at early follow-up. They returned to a mean of 51.3 ml/min at late follow-up. This decrease did not occur if the ischaemic period was 60 min or less.

Renograms (Figs. 5 and 6)

Overall function of the operated kidney decreased by a mean of 30% in the first week post-operatively but had returned to normal by one month and remained normal at late follow-up. There was a greater decrease in function post-operatively if the ischaemic period was more than 60 min and there was permanent functional loss in some kidneys. If the ischaemic period was less than 60 min, the function had returned to normal in the early post-operative period and remained at this level thereafter.

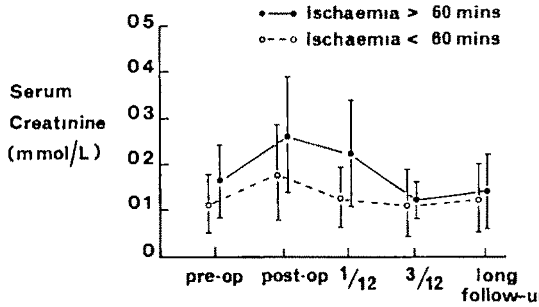

Fig. 2 Serum creatinine (mean ± SD) pre- and post-operatively in patients who had less than 60 min or more than 60 min ischaemia.

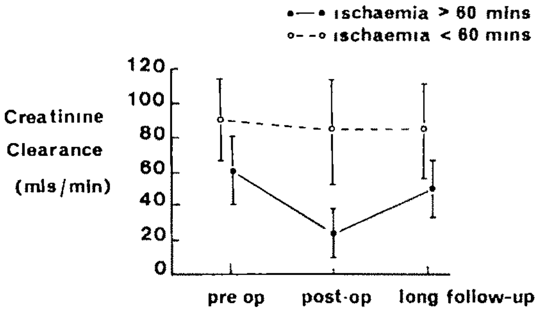

Fig. 4 Creatinine clearance (mean ± SD) pre- and post-operatively in patients who had less than 60 min or more than 60 min ischaemia.

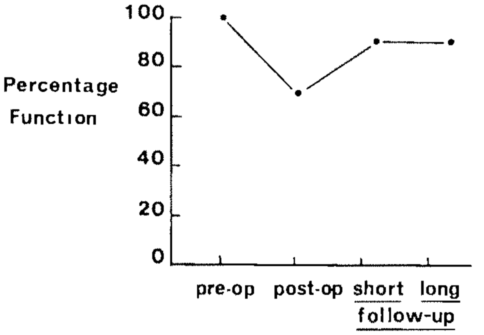

Fig. 5 Renograms: mean percentage renal function (of operated side) pre- and post-operatively in patients who had inosine.

Discussion

There can be no doubt that a 30-min period of warm ischaemia without protection causes a marked initial depression of renal function with a slow return towards normal. An ischaemic period of 60 min without protection causes a 70 to 80% initial depression of renal function; normal function may return later but more often there is a permanent loss of function which is either partial or total. The purpose of this study was to assess the value of inosine in preventing such ischaemic damage and to find its exact place in renal preservation.

Initial studies in experimental animals by Fernando *et al.* (1977) showed that plasma creatinine levels after intra-arterial or intravenous inosine and 60 min warm ischaemia were significantly lower than in controls. After 7 days creatinine clearances were higher than in controls and not different from clearance values in the normal kidney. Further studies (Wickham *et al.*, 1978, 1979) showed that inosine protected against *in situ* ischaemic renal damage for periods of up to 60 min, but did not prevent warm ischaemic damage in renal transplantation (Fitzpatrick *et al.*, 1981).

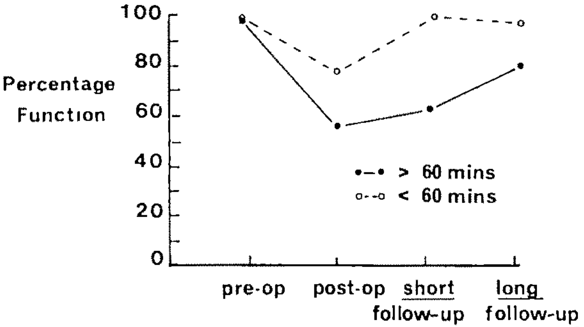

Fig. 6 Renograms: mean percentage renal function (of operated side) pre- and post-operatively in patients who had less than 60 min or more than 60 min ischaemia.

Marberger *et al.* (1980) found inosine to be effective in protecting against ischaemic damage, but less so than hypothermia. They showed that inosine was relatively ineffective in kidneys subjected to 2 to 3 h of warm ischaemia, but that the majority of kidneys subjected to 90 min of warm ischaemia with inosine protection could have a further 90 min of cold ischaemia without severe renal damage. These authors also suggested that 60 min of warm ischaemia was the limit of inosine protection.

The mechanism of this protection has been much discussed. It was originally suggested that inosine protected the renal brush border by providing high-energy phosphate to the ischaemic cell and provided a high concentration of ATP for the rapid post-ischaemic turnover of energy (Fernando *et al.*, 1976, 1979); the method whereby inosine entered the ischaemic cell was uncertain.

It would now seem more logical to suggest that inosine has a more general effect, either vasodilating hypoxic blood vessels (Bloom *et al.*, 1977) or preventing post-ischaemic vasoconstriction (Kashagarian *et al.*, 1976). Another possible action is that it protects and stabilises red cell membranes, thus preventing damage to them.

Inosine is a valuable addition to renal preservation in *in situ* ischaemia. The simplicity of its use by injection into a peripheral vein prior to ischaemia and the reliability of its protection for warm ischaemic periods of up to 1 h (particularly if pre-operative renal function is normal) have contributed to its usefulness. There was no late deterioration of renal function in the cases in which it was used.

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Conservative Surgery of Renal Carcinoma: The EIRSS Experience

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Summary—Seventy-two patients with renal carcinoma (RC) in a solitary kidney or bilateral synchronous tumours underwent parenchyma-sparing excision of their neoplasms. This was performed *in situ* in 51 and extracorporeally in 21 kidneys, with a complication rate respectively of 17 and 43%. The 5-year survival rates were 78% for unilateral disease, 48% for bilateral synchronous and 38% for bilateral asynchronous disease.

Survival correlated with *P* category, grade and diameter of the tumour. Vascular invasion and spindle cells indicated a poor prognosis; the position of the tumour, oncocytic elements, calcification, lymphocytic infiltration or the predominance of clear cell or granular cells did not influence survival.

In renal carcinoma (RC) without non-resectable metastases perifascial nephrectomy with primary control of the renal vessels and adrenalectomy is today considered the standard therapy: controversy exists only as to the appropriate extent of regional lymphadenectomy (Droller, 1980). With an absent or poorly functioning contralateral kidney, however, or bilateral tumour involvement, the need to preserve renal function limits the available treatment options. Fortunately, less than 2% of all patients with renal cancer fall into this category, thus limiting most urologists' experience of this problem to anecdotal cases. The European Intrarenal Surgical Society (EIRSS) therefore conducted a retrospective study among its members to evaluate the different treatment methods, in particular conservative surgery, in a larger patient population.

Patients and Methods

Seventy-two patients (41 males, 31 females) aged 37 to 72 years (mean 58.9) were admitted to the study; 18 had synchronous bilateral RC and 18 had RC in a solitary kidney after the contralateral kidney had been removed for RC 1 to 14 years previously. Patients with von Hippel-Lindau syndrome or RC with tuberous sclerosis were not included. Fifteen patients with RC in a solitary kidney had lost the contralateral kidney because of benign disease and in 18 it was so severely damaged that it was considered to be inadequate to sustain renal function. Three patients had a normal contralateral kidney but were submitted to conservative surgery because of apparently very localised tumours.

Sixty-nine patients were free of non-resectable metastases and subjected to an attempt at curative surgery; 3 patients had non-resectable solitary metastases, but were thought to be likely to benefit from removal of the primary tumour. Renal carcinoma was confirmed histologically in all. They were followed-up until their death (28 patients) or for a minimum of 12 post-operative months (24 patients>36 months; 15 patients 62-142 months).

Representative slides of the original specimens of 62 patients were available for histological re-evaluation by the reference pathologist (R.C.B.P.). The material was graded according to the criteria of Thackray (1964) and scrutinised for the predominant cell type, lymphocytic infiltration, calcification and vascular invasion in the tumour and kidney.

All data were collected on detailed flow-sheets

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table Complications of Conservative Surgery

	In situ *n*=*46**	*Ex situ* *n*=*21*
Haemorrhage	2	2
Renal artery/vein thrombosis	—	2
Femoral vein thrombosis	—	1
(Temp.) renal failure, dialysis	2	5
(Temp.) urinary extravasation	3	3
GI haemorrhage	1	—
Ureteric stenosis	1	1
Secondary nephrectomy	1	2
Patients with complications	8 (17%)	9 (43%)
Operative mortality	1 (2%)	0

* In 51 kidneys (5 patients underwent nephrectomy and are not listed here).

for every patient and transferred to punch cards for computer analysis. Survival curves were calculated using Kaplan-Meier's product-limit-estimate (Kaplan and Meier, 1958) and analysed with the Mantel-Cox and Breslow tests for non-parametric analyses of censored data. Trend analyses were performed with a modification of the generalised Kendall's tau test (Schemper, 1981).

Results

Tumours were excised from a kidney *in situ* in 46 patients and extracorporeally, with subsequent autotransplantation of the remaining kidney, in 21 patients. The surgical techniques have been described in detail elsewhere (Wickham, 1975; Marberger, 1980; Petterson and Brunger, 1981). The Table lists the post-operative complications and Figure 1 the serum creatinine values. The 2 groups are not strictly comparable, as the most advanced and technically difficult lesions were in the second, which included 18 patients with bilateral synchronous or asynchronous RC (compared with only 18 in the *in situ* group). In 5 patients conservative surgery appeared impossible and they were subjected to radical nephrectomy and chronic haemodialysis. One kidney could not be cleared of tumour at "bench" surgery, but was reimplanted as the patient was not accepted for haemodialysis. Five patients with synchronous bilateral RC underwent bilateral tumour excision, and 11 unilateral tumour excision and contralateral radical nephrectomy; this was performed simultaneously in 4 patients and staged in the others. Two patients died before the other kidney was removed.

Figure 2 gives the overall survival curves. Of 6 patients on chronic haemodialysis one died of metastatic disease 6 months post-operatively, and 4 of typical complications of haemodialysis without signs of RC 1 to 20 months post-operatively. One patient died of renal failure from progressive chronic pyelonephritis after 72 months and was tumour-free; 3 other tumour-free patients died from unrelated causes. Local recurrences were diagnosed after 6 to 29 months in 6 kidneys (4 autotransplanted) and were excised in 3. An autotransplanted kidney was removed and the patient received a cadaver kidney after 6 months of haemodialysis. He is the only survivor with a local recurrence, now 57 months post-operatively.

In 5 patients metastases in an adrenal gland or bone were removed at the time of primary surgery. In 3 other patients this was technically impossible. Lymph node metastases were found and excised completely in 3 patients and incompletely in one. All patients with distant metastases died of the disease 3 to 43 months post-operatively and only one patient remains alive 18 months after the removal of positive lymph nodes. Metastases appeared in 17 patients 3 to 61 months after

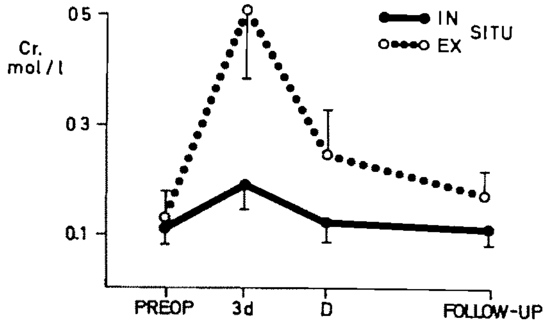

Fig. 1 Pre-operative and post-operative serum creatinine (M ± SEM) in patients with solitary kidneys.

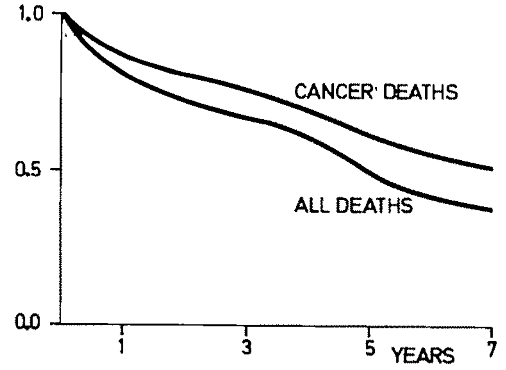

Fig. 2 Overall survival (smoothed Kaplan-Meier curves).

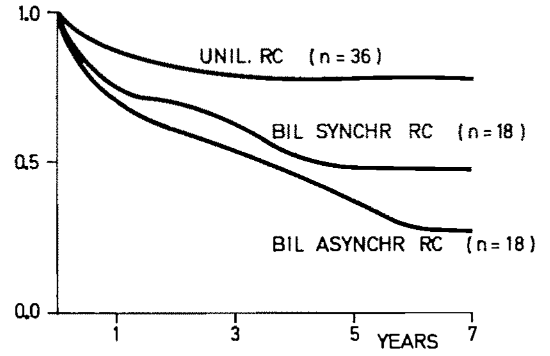

Fig. 3 Survival of patients with unilateral and bilateral synchronous and asynchronous renal carcinoma.

primary surgery. Only one of these patients is still alive, 74 months after removal of the primary tumour and 14 months after diagnosis of chest metastases. Attempts at radical excision in 4 patients failed to control the disease.

Plotted on a logarithmic scale, the overall cancer survival curve appears nearly linear, suggesting a constant hazard of tumour death during the first 5 years of follow-up. The conservative procedures were combined with a formal lymph node dissection in 23 instances, but this had no positive effect on the survival curves.

Patients with renal carcinoma in a solitary kidney, whose contralateral kidney had been removed previously because of RC (=asynchronous bilateral RC), had a significantly poorer survival than patients without malignant contralateral disease (Fig. 3). Prognosis did not correlate with the time interval between treatment of the asynchronous tumours ($P = 0.2$), and there was no significant difference in survival between synchronous and asynchronous bilateral RC ($P > 0.4$).

Prognosis correlated significantly with the extent of local tumour spread as defined by the P category (UICC, 1974) of the surgical specimen (Fig. 4) and the tumour diameter ($P = 0.025$). Of 24 patients with tumours of a diameter < 6 cm only one with asynchronous bilateral RC died of the tumour, 66 months after *in situ* excision. In the group of 28 patients with unilateral P1 and P2 RC only 3 died; in one bone metastases were present at the time of diagnosis and one died following renal artery thrombosis complicating haemodialysis (Fig. 5). The presence or site of multiple tumours within the kidney did not influence the outcome.

Tumour grade had a significant impact on survival. Three patients had low, 52 average and 7 high grade tumours. All patients with low grade RC survived, whereas 4 of 7 patients with high grade tumours died within 12 months. Pure clear cell RC did not have a better prognosis than the other tumours, nor was survival influenced by the appearance of granular cells, oncocytic elements, calcification or lymphocytic infiltration. Four of the 6 patients with spindle cell elements in their tumours died within 16 months of operation. Patients whose specimens showed vascular invasion in the tumour or kidney survived less well ($P < 0.05$) and all 6 patients with major tumour invasion of the renal vein or vena cava died of the disease within 6 to 20 months (Fig. 6).

Discussion

The tumours observed in this series did not differ in morphology and behaviour from RC as usually seen in the presence of a normal contralateral kidney. An apparently better prognosis of bilateral synchronous RC, as Jacobs *et al.* (1980) concluded from tracing the fate of patients reported in the literature, could not be confirmed. Aside from a possible bias in patient selection,

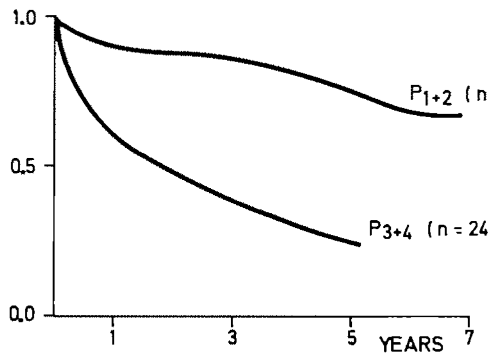

Fig. 4 Survival of all patients correlated with P category.

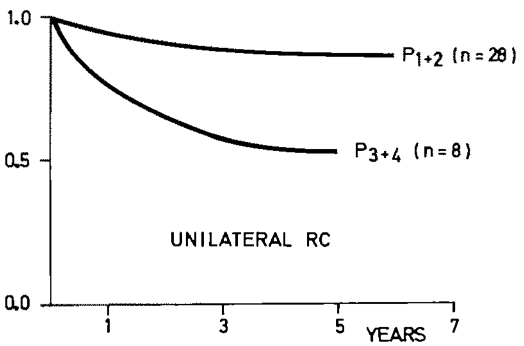

Fig. 5 Survival of patients with unilateral renal carcinoma correlated with P category.

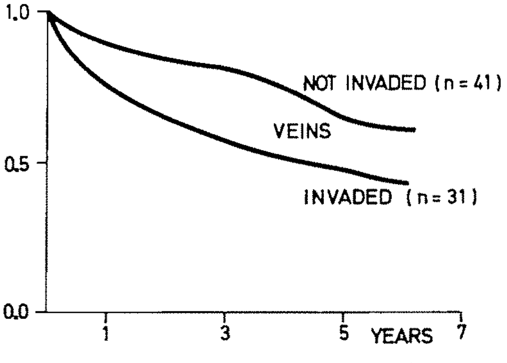

Fig. 6 Survival correlated with vascular invasion in tumour and kidney.

their study included 20% tumour with hereditary background, which are known to behave less aggressively (Pearson *et al.*, 1980).

The prognosis of patients with untreated RC is gloomy, with a 5-year survival rate of less than 30%, and of less than 6% in the presence of metastases (Marberger, 1980); the figures can be assumed to be even worse with an absent or diseased contralateral kidney. Although an exceptional long-term survivor has been reported after radiotherapy, chemotherapy or hormonal therapy, only surgical excision offers a reasonable chance of cure. In Wickham's (1975) survey of the English literature 75% of 30 patients with RC in a solitary kidney treated non-surgically died within a mean follow-up period of 24 months, and all 16 patients with bilateral synchronous RC within 5 months.

The experience presented here clearly demonstrates that parenchyma-sparing excision of the tumour is the treatment of choice. Eighty-seven per cent of all non-metastatic RC with a diameter of less than 7 cm have an unperforated pseudocapsule, which provides an ideal plane of cleavage for complete excision (Rocca Rossetti, 1981). Larger tumours frequently infiltrate the structures at the base of the tumour but, with a wedge excision of marginal parenchyma, radical removal as demonstrated by frozen sections is frequently achieved. Extracorporeal "bench" surgery does not prevent local recurrences or metastatic spread. In view of its higher morbidity it should therefore be limited to rare central tumours requiring extensive reconstruction of hilar structures, in which, however, it may still give the patient a chance of cure (Roehl *et al.*, 1981).

Radical nephrectomy and haemodialysis cannot be considered as alternatives to conservative surgery because of excessive morbidity. Renal allografting should not be performed before the patient has survived tumour-free for at least 12 months (Penn, 1977).

The survival rates achieved with conservative surgery in this series are encouraging and fully justify the aggressive approach, so long as metastases can be ruled out. Our results confirm other favourable reports on smaller series (Schiff *et al.*, 1979; Jacobs *et al.*, 1980) and shed some doubt on the need for radical nephrectomy for small peripheral RC in the presence of a normal contralateral kidney. With the increased availability of sonography and CT scanning these tumours are detected more frequently. As the diameter is a good prognostic parameter, conservative surgery appears permissible for selected lesions of this type.

Acknowledgement

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Hepatic Dysfunction in Renal Carcinoma

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Summary—In a retrospective review of 81 patients with renal carcinoma 34 (42%) had abnormalities of one or more liver function tests. Fifteen patients (18.5%) had abnormalities of 3 or more liver function tests but without evidence of hepatic metastases. There was a significant association between these patients and the presence of fever, anaemia, weight loss and a raised ESR ($P<0.001$) compared with those whose liver function was normal. Following nephrectomy, liver function returned to normal in 5 patients. Median survival in these patients was 35 months, whilst in those whose liver function remained abnormal the median survival was 8 months ($P<0.01$).

It is well known that many patients with renal carcinoma do not present with urological symptoms and that the variety of symptoms and signs are due to the non-specific "toxic" effects of the tumour, the presence of metastases or the specific effects caused by ectopic hormonal production (Altaffer and Chenault, 1979). The syndrome of non-metastatic hepatic dysfunction was first described in 5 patients with renal carcinoma who developed hepatomegaly and abnormal liver function without evidence of hepatic metastases (Stauffer, 1961). An incidence of 4 to 15% has been subsequently reported in the literature (Walsh and Kissane, 1968; Warren *et al.*, 1970; Ramos and Taylor, 1972; Strickland and Schenker, 1977; Boxer *et al.*, 1978) but little information has been given about the outcome, and the significance of this condition remains uncertain.

The aim of the present study was to document the incidence of hepatic dysfunction in a series of patients with renal carcinoma and to determine whether it was of any prognostic significance.

Patients and Methods

The clinical records of 81 patients with primary renal carcinoma presenting between 1971 and 1980 have been retrospectively reviewed and the symptoms, signs, laboratory investigations, radiological and operative findings and pathology recorded for analysis. Abnormalities of liver function were determined by elevation of serum alkaline phosphatase, γglutamyl transferase, bilirubin and SGOT, lowered serum albumin, abnormal globulins on electrophoresis and a prolonged prothrombin time.

A diagnosis of non-metastatic hepatic dysfunction was made on the basis of abnormalities of 3 or more tests and the exclusion of hepatic metastases by liver scan, aortography, biopsy and findings at laparotomy.

Survival data were analysed by life table analysis and the log rank test (Peto *et al.*, 1977) and the clinical features compared by the χ-square test, with Yates's correction for small numbers.

Results

There were 48 men and 33 women with a mean age of 58.7 years (range 25-81). A minority of patients presented with urological symptoms and 20 (25%) had symptoms due to metastatic disease (Table 1).

Thirty-four patients (42%) had abnormalities of one or more liver function tests (Table 2). The alkaline phosphatase was abnormal in one-third of the patients and an abnormal pattern of $\alpha 2$ globulin found on electrophoresis in nearly 70% of the patients in whom it was measured. Hepa-

Table 1 Presentation of 81 Cases of Primary Renal Cell Carcinoma 1971-80

	No.	*(%)*
Haematuria	26	(33)
Mass	23	(29)
Classical triad (loin pain, mass, haematuria)	5	(6)
Metastatic disease	20	(25)

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Table 2 Abnormalities of Liver Function

	No of tests performed	*Abnormal*	
		No.	*(%)*
Serum alkaline phosphatase	71	34	(47)
Serum γglutamyl transferase	35	13	(37)
Serum albumin	65	7	(11)
Serum α2 globulin	13	9	(69)
Serum bilirubin	63	4	(6)
Prolonged prothrombin time (>3 s)	26	5	(19)

Hepatomegaly 7, splenomegaly 2.

tomegaly was noted in 7 patients (by clinical examination in 4 and on scanning in 3) and splenomegaly in 2 patients. Seven patients had radiological or histological evidence of bone metastases in the presence of an elevated alkaline phosphate (Table 3) and hepatic metastases were discovered in 4 patients (by arteriography in one, biopsy in one and at laparotomy in 2). Four patients had an elevation of alkaline phosphatase as the only abnormality but iso-enzymes and γglutamyl transferase were not measured in these patients.

Fifteen patients (18.5%) had abnormalities of 3 or more liver function tests without clinical, radiological or histological evidence of hepatic metastases and were classed as having the syndrome of non-metastatic hepatic dysfunction.

Significant variables in presentation between those with and without hepatic dysfunction are shown in Table 4. Fever, anaemia, weight loss and a raised ESR were statistically more commonly associated with hepatic dysfunction ($P<0.001$) but there were no differences between patients with and without hepatic dysfunction in terms of stage of disease.

Only 13 of the 81 patients (16%) remain alive. There are no long-term survivors in the patients with advanced disease. The median survival of patients with and without hepatic dysfunction is almost identical (19.6 months and 20.8 months respectively). Two of the patients with the syndrome of non-metastatic hepatic dysfunction died in the early post-operative period but without evidence of liver metastases at autopsy and one died without surgery being performed. Liver function remained abnormal in 7 patients following nephrectomy and the median survival of these was 8 months, whilst in the 5 patients whose liver function returned to normal the median survival was 35 months ($P<0.01$). All of the patients whose liver function remained abnormal died with recurrent or metastatic disease, although in 2 there was no evidence of liver metastases at autopsy. Of the patients whose liver function reverted to normal one is alive at 36 months, one died of unrelated causes at 30 months, one died at 6 months from local recurrence but without evidence of widespread disease and 2 died at 42 and 60 months from disseminated disease. In the patient who died at 60 months liver function again became abnormal terminally.

Table 3 Cause of Abnormal Liver Function Tests

	No.
Bony metastases with an elevated alkaline phosphatase	7
Isolated elevation of alkaline phosphatase	4
Hepatic metastases	4
Local recurrence	4
Non-metastatic hepatic dysfunction	15
Total	34

Table 4 Significant Features of Renal Carcinoma in Patients With and Without Non-Metastatic Hepatic Dysfunction

	Without n=66		*With n=15*	
	No.	*(%)*	*No.*	*(%)*
Haematuria	20	(31)	6	(40)
Loin pain	12	(18)	4	(27)
Mass	15	(23)	8	(53)
Fever	2	(3)	7	(47)*
Anaemia	9	(14)	10	(67)*
Weight loss/malaise	7	(4)	7	(47)*
Raised ESR	13	(20)	11	(73)*

*$P<0.001$.

Discussion

The variable incidence of hepatic dysfunction probably reflects the extent to which the patients are investigated. Utz *et al.* (1970) reported that 40% of their patients seen since 1961 had 3 or more abnormal liver function tests and the incidence in our patients of 18.5% occurred during a period in which nearly all patients had routine pre-operative liver function tests. In contrast to other studies, the bilirubin and SGOT were almost invariably normal.

This study has also provided further evidence of the association of this syndrome with the presence of fever, anaemia, weight loss and a raised ESR. These features are present in a high proportion of cases and may form part of the syndrome (Strickland and Schenker, 1977).

The most consistent abnormality in this and other series was an elevated alkaline phosphatase. A variant of this enzyme has been found to be released from neoplastic tissue and it has been suggested that ectopic production by the tumour may be the explanation for this occurrence (Durocher, 1969; Stolbach *et al.*, 1969). There are few reports of the isoenzymes of alkaline phosphatase but in the latter part of our series there was usually a coexistent elevation of the γglutamyl transferase and this suggests a hepatic origin for the enzymes. Two patients with abnormal liver function tests were found to have hypercalcaemia and although calcium levels became normal following nephrectomy, liver function remained abnormal. Increased liver lysosomal activity has also been found in patients with renal cell carcinoma (Schersten *et al.*, 1969). Increased platelet counts have been previously noted in association with the hepatic dysfunction syndrome (Walsh and Kissane, 1968; Tartaglia *et al.*, 1970; Ramos and Taylor, 1972) but in most instances was not observed in this study and it may just represent a non-specific association with malignant disease (Leven and Conley, 1964). Increased α2 globulin levels have been reported as part of a triad with fever and anaemia in renal carcinoma (Bowman and Martinez, 1968) and as a reliable indicator of prognosis (Chisholm, 1980) but this may also occur as part of an acute phase protein reaction in response to tissue necrosis (Darcy, 1964). The hepatic dysfunction syndrome has also been reported in association with xanthogranulomatous pyelonephritis (Vermillion *et al.*, 1970) and this could also represent a non-specific reaction in response to necrotic tissue.

There did not appear to be any marked differences in histological type of the carcinoma in those with and without hepatic dysfunction in our patients. Bottiger *et al.* (1966) suggested that 2 distinct histological types of renal carcinoma occurred with characteristic biochemical changes. The group with a predominantly clear cell type of tumour, containing PAS positive material in the cytoplasm, had significant increases in ESR, serum α2 globulin and haptoglobin levels. These reverted to normal following nephrectomy and metastases were less common in this group than in those with mainly PAS negative granular cells.

The outcome of the hepatic dysfunction following nephrectomy is variable. In a review of the syndrome Strickland and Schenker (1977) applied rigid diagnostic criteria and stated that either reversible hepatic dysfunction or unequivocal evidence of the absence of metastases was a prerequisite for the diagnosis. Greenberg *et al.* (1964) quoted the 10 cases reported by Stauffer (1961), who stated that hepatic dysfunction became normal in all following nephrectomy. Warren *et al.* (1970) reported that 13 out of 60 patients had reversal of hepatic dysfunction and 11 of these were alive, whilst in 14 patients whose liver function did not revert to normal only 4 were alive. Ramos and Taylor (1972) reported reversal in 4 out of 5 patients, but 3 of these died in less than one year from metastatic disease. Boxer *et al.* (1978) did not specify the outcome in their patients but only one survived long term. In our series there was a statistically significant difference in survival between those whose hepatic function returned to normal and those where it remained abnormal ($P<0.01$). Of crucial importance to this issue is the presence of occult hepatic metastases. These were excluded as stringently as possible by liver scanning, biopsy, arteriography and the appearances at laparotomy. Review of the literature suggests that there are no characteristic changes in liver histology in this condition and the appearances may be entirely normal or show areas of focal necrosis, fatty change or lymphocytic infiltration (Strickland and Schenker, 1977).

Arteriography, whilst demonstrating pathological circulation in the liver if metastases are present, may also reveal typical appearances of hypervascularity and hepatomegaly (Mena *et al.*, 1974).

The aetiology of this syndrome remains speculative and the possibility that it results from occult hepatic metastases which regress following nephrectomy appears unlikely. Toxin production by the tumour could produce abnormal effects on liver function but attempts to reproduce the syndrome in experimental animals have been unsuccessful (Hanash *et al.*, 1971). Some of the effects could be due to a non-specific reaction to cell necrosis and this could also explain the occurrence in granulomatous pyelonephritis. The consistent finding of abnormal globulin suggests that the syndrome may have an immunological basis, but few studies of immunoglobulins have been reported in detail. Hemmingsen and Skarrup (1977) have shown that in nearly 75% of patients with renal carcinoma there was a glomerular type of proteinuria with significant losses of albumin, haptoglobin and immunoglobulins compared with controls and it was thought this was due to an immune complex type glomerulonephritis in response to tumour derived antigens (Cummings *et al.*, 1974). Failure of liver function to revert to normal following removal of the primary tumour may thus indicate that there remains an undetected extra-renal tumour mass which is still able to exert its effect on liver function.

This syndrome thus represents a further example of the capricious nature of renal carcinomas. Abnormal liver function in such patients does not necessarily imply the presence of metastases but failure of reversion to normal following nephrectomy is clearly of grave prognostic significance.

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The Late Results of Conservative Surgery for Upper Tract Urothelial Carcinomas

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Summary—In a selected series of 14 patients, upper tract urothelial tumours were excised with preservation of the ipsilateral kidney. The 5-year survival rate was 83%. The ipsilateral local recurrence rate was 5/14 (36%) but in 4 cases salvage surgery was effective and in 2 cases a functioning kidney was still preserved. The results of conservative surgery and its indications are discussed.

The management of urothelial carcinomas of the renal pelvis and ureter retains one major point of controversy—is the standard operation of nephroureterectomy an unnecessarily wide clearance and is the sacrifice of a kidney essential for a tumour which could have been excised with conservation of the kidney? The basis for advocating nephroureterectomy for all upper tract tumours is the well established multifocal nature of urothelial malignancy, the low incidence of contralateral upper tract tumours (Bloom *et al.*, 1970; Latham and Kays, 1974, Rubenstein *et al.*, 1978), the high incidence of ureteric stump recurrences (Kinder and Wallace, 1962; Strong and Pearse, 1976) and of subsequent bladder tumours (Williams and Mitchell, 1973). The standard operation of nephroureterectomy with a cuff of bladder gives an adequate clearance for a multifocal tumour, but gives a poor clearance for infiltrating tumours along the pathway of spread via the pelvic or para-aortic nodes. As with urothelial carcinomas of the bladder, the grade of tumour and the depth of invasion are the important prognostic factors. Patients with high grade invasive tumours are likely to die from metastatic disease before developing local recurrences, and patients with non-infiltrating well differentiated tumours may follow a relatively benign course (Murphy *et al.*, 1980, 1981).

Localised excision is possible in a proportion of upper tract tumours with conservation of the kidney. This was first reported by Vest (1945) and has been the subject of several reports since. These tumours are uncommon and in most series the numbers are small, the selection of cases is obscure and the causes of failure not clearly documented. It is unlikely that sufficient numbers will ever be collected for a prospective trial to determine the indications for and the results of conservative surgery.

We report the results of a series of conservative operations done over a 21-year period with analysis of the outcome.

Patients and Methods

Fourteen patients with upper tract urothelial carcinomas were treated by conservative surgery between 1956 and 1977. All were followed for a minimum of 4 years with a mean follow-up period of 7.8 years. Six patients were treated at the Royal Marsden Hospital and 8 at St Bartholomew's Hospital. The Royal Marsden Hospital is a referral centre for urological oncology and the cases are therefore selected, while St Bartholomew's Hospital is a general urological unit. All of the records of the Department of Urology at St Bartholomew's Hospital have been computerised since 1970. From the 9500 completed records there were 593 urothelial carcinomas of which 38 involved the upper urinary tracts. Conservative surgery was performed in 9 of these cases, but in one patient the follow-up period is too short and he is not included.

There were 3 female and 11 male patients with a mean age on diagnosis of 61 years (range 35-75). Two patients had had contralateral nephroureter-

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ectomies for tumours 2 and 6 years previously. None had evidence of renal impairment or analgesic nephropathy. Urine cytology was performed in 8 cases and was positive in 6. The 2 patients with falsely negative urine cytologies both had well differentiated tumours.

The sites of the initial tumours are shown in Table 1 and the operations performed are listed in Table 2. Thirteen tumours were transitional cell carcinomas and there was one squamous cell carcinoma. Seven tumours were well differentiated (G1), 6 were moderately differentiated (G2) and one was poorly differentiated (G3).

Results

The details for all cases are shown in Table 3. Ten patients are still alive after a mean follow-up period of 7.7 years. Eight still have a functioning kidney on the side operated upon. Five years after operation, 10 out of 12 patients were still alive, giving a crude 5-year survival rate of 83%.

Two patients died of metastatic disease and 2 died without evidence of urothelial cancer. One died after 18 years and one died after 2 years from a myocardial infarct; no evidence of urothelial malignancy was found at post mortem examination.

Ipsilateral Recurrent Upper Tract Tumours

Five patients developed ipsilateral recurrent upper tract tumours 2 to 11 years after operation. Since these cases represent failure of conservative surgery, their details are summarised.

Case 1. Presented with multiple small tumours around the left ureteric orifice and with tumour in the lower left ureter. The bladder tumours were treated endoscopically and the lower left ureter was excised and reimplanted. The tumour in the ureter was shown to be moderately differentiated (G2) and to have invaded muscle, but tumour also extended to the cut edge of the ureter. He continued to have recurrent bladder tumours for a further 2 years and when his bladder was clear, a follow-up IVU showed recurrent tumour in the renal pelvis and ureter. Following a left nephroureterectomy he continued to develop recurrent bladder tumours for 2 years, but has now been recurrence-free for a further 2 years.

Table 1 Site of First Upper Tract Tumours

Pelvis with caliceal extension	4*
Pelvis and pelviureteric junction	3
Lower third of ureter	7
Total	14

* One patient had synchronous bilateral tumours in the lower moieties of bilateral duplex systems.

Table 2 Conservative Operations Performed

Partial nephrectomy	4
Local excision of pelvis	3
Excision of lower ureter with:	
reimplantation of ureter	5
transureteroureterostomy	1
End-to-end anastomosis	1
Total	14

Case 2. Presented with a tumour in the upper moiety of a duplex left kidney. A partial nephrectomy was performed. Histological examination showed multifocal tumour extending to the ureteric and caliceal resection lines. He subsequently developed tumours around the left ureteric orifice and his second annual follow-up IVU showed recurrent tumour in the lower ureter. The nephroureterectomy specimen showed tumour in the renal pelvis as well as ureter. He has continued to develop superficial bladder tumours which have been easily controlled endoscopically.

Case 3. Had a left nephroureterectomy for a tumour in the renal pelvis. Two years later a tumour was shown on IVU in the upper calix of the right kidney. This was treated by local excision. The tumour was well differentiated without invasion. She remained well for 11 years and then developed a tumour in the lower ureter. This was excised and the ureter reimplanted. The tumour was again well differentiated but had invaded submucosa and the resection edges showed atypia. She had one bladder tumour treated endoscopically 2 years later and 20 years after her first conservative resection her kidney is functioning well.

Case 4. Had had a left nephroureterectomy for tumour 6 years previously. He then presented with a tumour in the right renal pelvis. This tumour was excised from his renal pelvis and tantalum wire laid outside the pelvis to give a radiation dose of 6050 rads to the pelvis. Three years later he developed a severe stenosis of his pelviureteric junction and also recurrent tumour in the pelvis. The tumour was again excised and the kidney drained with a nephrostomy tube, since reconstruction was not thought possible because of massive peripelvic fibrosis. He lived a full active life for a further 18 years before dying of disseminated adenocarcinoma of uncertain origin.

Case 5. Was referred with tumours in both lower moieties of bilateral duplex systems. One year previously he had had a cystectomy for multiple bladder tumours which had not responded to radiotherapy or intravesical

Table 3 Analysis of the Features of the First Upper Tract Tumours and the Individual Results

Case	*Age*	*First upper tract tumour*			*First bladder tumour*	*Upper tract recurrence*	*Metastases*	*Survival*	*Follow-up (years)*
		Site	*Grade*	*Invasion*					
1	72	Ureter	G2	Muscle	Synchronous	Yes	None	Alive and well	6
2	61	Pelvis	G1	Submucosal	After	Yes	None	Alive and well	6
3	52	Pelvis	G1	None	After	Yes	None	Alive and well	20
4	35	Pelvis	G1	None	None	Yes	None	Died no evidence of disease	18
5	68	Bilateral pelvis	G2	Parenchyma	Before	Yes	Yes	Died	6
6	65	Pelvis	G3	Parenchyma	None	No	Yes	Died	2
7	69	Ureter	G2	Muscle	After	No	None	Alive and well	4
8	71	Pelvis	G1	None	None	No	None	Alive and well	8
9	52	Ureter	G1	None	None	No	None	Alive and well	4
10	64	Ureter	G2	None	None	No	None	Alive and well	9
11	75	Ureter	G1	None	Before	No	None	Alive and well	9
12	61	Ureter	G2	Submucosal	Before	No	None	Alive and well	7
13	62	Ureter	G2	Submucosal	None	No	None	Died no evidence of disease	2
14	44	Pelvis	G1	Submucosal	None	No	None	Alive and well	7

thiotepa. He was treated initially with methotrexate for a year and then by a left lower partial nephrectomy with local excision of tumours from the upper moiety. This was followed by combination chemotherapy and 2 years later a lower right partial nephrectomy was performed for progression of the tumours in the lower moiety. A para-aortic nodal mass was noted at operation. The left kidney was removed a year later as the lower ureter had become obstructed by tumour. He died 6 years after the first conservative operation on his left kidney and 8 years after the upper tract tumours were first diagnosed.

Bladder Tumours

The occurrence of bladder tumours in relation to the upper tract tumour is set out in the Figure. All bladder tumours were controlled by endoscopic resection and diathermy except for Case 5 and another patient, Case 7, who developed widespread symptomatic carcinoma *in situ* of the bladder 3 years after resection of a squamous carcinoma of the ureter. He was treated by cystourethrectomy after he had failed to respond to chemotherapy. The ureters showed no evidence of carcinoma.

Discussion

Other published series of conservative operations for upper tract urothelial carcinomas have been reviewed and summarised in Table 4. The results

Table 4 Collected Results Of Surgery Of Upper Tract Urothelial Carcinomas

Author	*Year*	*Number of cases*	*Ipsilateral recurrences*	*Deaths from malignant disease*	*5-Year survival*
Babaian	1980	9	0	0	9/9
Bloom	1970	12	1	NS*	5/7
Booth	1980	37	NS	NS	16/27
Brown	1974	4	1	0	3/3
De Wolf	1974	5	2	1	1/3
Gibson	1972	3	0	0	3
Hawtrey	1971	9	1	3	1/9
Mazeman	1976	117	27 (23%)	NS	NS
McIntyre	1965	8	1	2	5/8
Petkovic	1975	49	7/21 (33%)	NS	21/32 (66%)
Strong	1976	7	1	NS	NS
Vest	1945	3	0	0	1/1
Present study	1981	14	5 (36%)	2	10/12 (83%)

* NS—not stated.

BLADDER TUMOURS

Case No	Before	Synchronous	After	None
5	●			
11	●			
12	●	●	●	
2		●	●	
1			●	
3			●	
7			●	
4				●
6				●
8				●
9				●
10				●
13				●
14				●
	3	2	6	7

Fig. The occurrence of bladder tumours in relation to the upper tract tumours in the 14 cases

from this collected series of 267 patients are consistent. The 5-year survival rate was 75 of 111 patients (68%) and the ipsilateral recurrence rate was 60 of 208 patients (29%) while only 8 of 55 patients (14.5%) died of malignant disease. While the controversial aspects of conservative surgery are frequently discussed, the results of such treatment are seldom presented so that the causes of failure can be easily analysed.

The objective of conservative surgery was achieved in 10 of the 14 cases in this series, *i.e.* the ipsilateral kidney was preserved and tumour was cleared from that upper tract. In 4 cases conservative surgery failed. In Cases 1 and 2 the tumour was completely excised but microscopy showed inadequate clearance. Local recurrences occurred in each case 2 years later. Cases 5 and 6 had Grade 2 and 3 tumours infiltrating renal parenchyma. Case 6 died with metastatic disease without local recurrence but did not have either radiotherapy or chemotherapy. Inadequate clearance of a multifocal renal pelvic tumour may be the result of inadequate pre-operative assessment and the anatomical constraints placed on the surgeon at the time of operation. Inadequate clearance of ureteric tumours could be avoided with good radiology and frozen section examination of the cut ends of the ureters.

The incidence of bilateral tumours in several series where analgesic nephropathy and Balkan nephropathy were absent was between 1 and 5%. (Bloom *et al.*, 1970; Latham and Kays, 1974; Rubenstein *et al.*, 1978). The findings of 3 cases with bilateral tumours in this series is almost certainly due to the selection of cases referred to the Royal Marsden Hospital. The low incidence of contralateral tumours is weak evidence in favour of conservative surgery. However, when renal function is poor and there is a high risk of contralateral disease, as in Balkan nephropathy and analgesic nephropathy, then conservative surgery is indicated. Petkovic (1975) reported more patients with Balkan nephropathy dying from renal failure than from their malignant disease. Autotransplantation with calicovesicostomy, as reported by Pettersson *et al.* (1979), allows the maximum clearance of upper tract urothelium with endoscopic surveillance of the renal pelvis and calices.

In our series we selected for conservative surgery a high proportion of patients with low grade (G1) tumours. Three of the 4 patients in whom treatment failed had high grade tumours (G2 and G3). Pre-operative ureteric urine cytology has been shown to correlate well with the histological grade of the upper tract tumour and should therefore be routinely used when conservative surgery is contemplated (Zincke *et al.*, 1976).

When the tumour is poorly differentiated and infiltrating, the prognosis is extremely poor and the patient likely to die of metastastic disease irrespective of the nature of his operation. If sacrifice of the kidney is not essential to obtain adequate clearance, then this may considerably facilitate subsequent chemotherapy and may influence survival.

We would therefore propose the following indications for conservative renal surgery: (1) solitary kidneys, (2) bilateral synchronous tumours, (3) significant impairment of (total) renal function, (4) well localised tumour, (5) urine cytology indicates that the tumour is of low grade.

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Improvement in Renal Function Following Ureteric Reimplantation for Vesicoureteric Reflux

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Summary—Ten children with vesicoureteric reflux who had moderate impairment of renal function before corrective surgery have been analysed retrospectively. A significant improvement in renal function occurred after successful anti-reflux surgery. The possible reasons for this improvement are discussed with emphasis on the functional rather than the morphological effects of reflux.

The management of children with "primary" vesicoureteric reflux (VUR) is controversial. In an excellent review of the subject, Ransley (1978) discussed the pathophysiology, natural history and treatment of VUR with particular reference to the association of intrarenal reflux and urinary infection with subsequent scar formation. The basis of this "big bang" theory, in which both urinary infection and intrarenal reflux are necessary prerequisites for renal damage, is essentially morphological. Ransley, in his review, discussed the problems in determining the effects of VUR on renal function and, in contrast to the morphological consequences, the functional consequences have been largely overlooked.

In an attempt to determine the effects of VUR on renal function, we have reviewed our experience of the surgical treatment of children with VUR who had objective evidence of impaired renal function at the time of presentation.

Patients and Methods

Between October 1972 and July 1979, 73 children under 14 years of age had surgical correction of VUR. Of these, 17 (23%) had objective evidence of impaired renal function before operation as judged by a Cr51-EDTA glomerular filtration rate (GFR) of less than 80 ml/min, when corrected to a body surface area of 1.73 m^2, and a serum creatinine above the upper limit of normal for a child of that age. Ten of these 17 children had bilateral VUR with no evidence of coexisting urological disease (*e.g.* urethral valves, neuropathic bladder) and with sufficient information available in their case notes for adequate retrospective analysis.

There were 7 boys and 3 girls aged 3 to 13 years (mean 5.5 years). All had a history of bacteriologically proven urinary infection, proven bilateral VUR on micturating cystography and some degree of renal scarring of both kidneys on intravenous urography.

The surgical treatment in 7 children was bilateral ureteric reimplantation by either the Politano-Leadbetter ureteroneocystotomy (Politano and Leadbetter, 1958) or the Cohen advancement technique (Cohen, 1975). In 3 children, the pre-operative Tc^{99m}DMSA renal scan showed one kidney to contribute less than 15% to overall renal function, and these children were treated by nephroureterectomy and contralateral ureteric reimplantation. All of the children had had sterile urine for at least 3 months prior to the estimation of their GFR and their subsequent operation.

In every case, follow-up assessment showed that the VUR was cured. There were no post-operative complications. Prophylactic antibiotics were given for 3 to 6 months post-operatively and were then discontinued. All 10 children have been followed up for at least one year and 7 of the children for at least 2 years.

Results

All 10 children are alive and well, although one child requires drugs to control hypertension. All have shown some degree of improvement in renal function with time (Figs. 1 and 2).

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

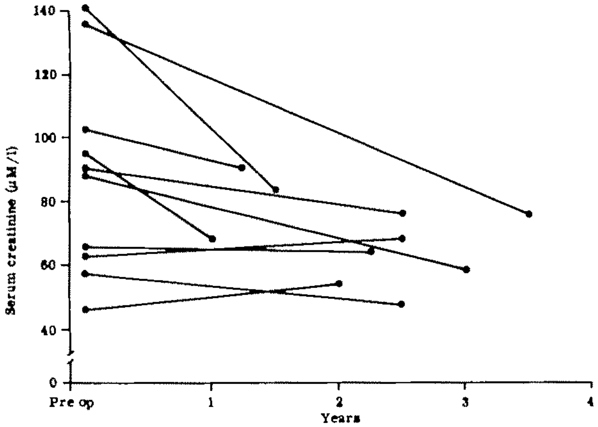

Fig. 1 Serum creatinine levels (μmol/l) of the 10 children before anti-reflux surgery and 1 and 2 years post-operatively

The improvement in the GFR was greater than the improvement in the serum creatinine. This is to be expected as the serum creatinine increases with age in young children, thus reducing the fall that occurs with improving renal function, whereas the GFR is corrected for body surface area.

A statistical analysis of the changes in these 2 measurements is shown in Figure 3. Using Student's t-test for paired samples, the improvement in the serum creatinine was significant at the 5% confidence level and the improvement in the GFR at the 1% confidence level at both 1 and 2 years after operation.

A comparison of the pre-operative and post-operative Tc^{99m}DMSA renal scans in those children having bilateral ureteric reimplantation has shown no significant change in split function.

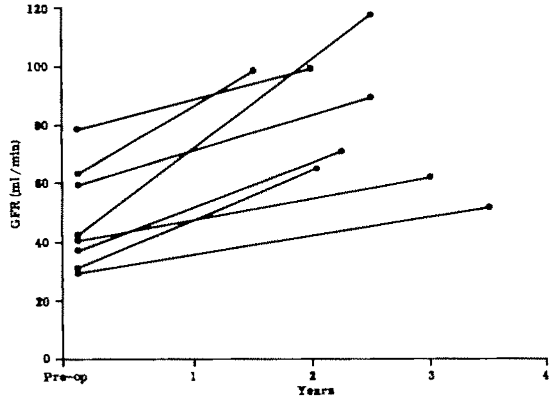

Fig. 2 Glomerular filtration rate of 8 of the 10 children (corrected to a body surface area of 1.73 m^2) before anti-reflux surgery and 1 and 2 years post-operatively. In 2 children a pre-operative GFR was not obtained.

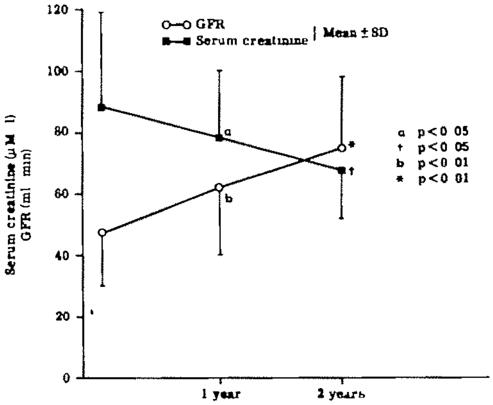

Fig. 3 Serum creatinine (10 children) and GFR (8 children) before anti-reflux surgery and 1 and 2 years post-operatively. (Mean levels ± SD for the children as a group and the statistical significance of the changes seen.)

Thus the improvement in overall renal function would seem to be due to an improvement in the function of both kidneys.

Discussion

These results demonstrate that in children with VUR who have impaired renal function, improvement in function can be expected after surgical correction. What is not known is whether this improvement in function can be equalled or bettered by conservative management in a matched group of children. Furthermore, although the children presented here were not consciously selected, a retrospective analysis such as this is always open to criticism on the grounds of patient selection. Nevertheless, it is felt that the conclusion that surgical correction of VUR in children with impaired renal function may lead to improvement in renal function is a valid observation, particularly as all the children were past the age at which spontaneous improvement of renal function, due to maturation, might have occurred. This observation may be an important factor in deciding whether or not to operate on a child with VUR regardless of control of urinary infection.

The reason for the post-operative improvement in renal function is not clear. Hutch and Smith (1969) suggested that sterile reflux, although less damaging to the kidney than infected reflux, was nevertheless harmful. Orr *et al.* (1971), on the basis of experiments with a canine model of VUR, suggested that this harmful effect might be due to alterations in renal blood flow that occurred as a consequence of reflex. In a more detailed experimental study using piglets, Helin *et al.* (1975) found that after 3 to 4 months of sterile reflux, the affected kidneys showed a reduced capacity to maintain a steady blood flow when intravesical pressure was elevated during voiding and that both the glomerular and tubular function of these kidneys had decreased by about 50%. All of these reports have drawn analogies between VUR, especially during voiding, and partial or intermittent ureteric obstruction.

We have insufficient data to propose an explanation for the improved renal function seen in these children after operation, since studies of renal blood flow and tubular function were not performed. However, as follow-up Tc^{99m}DMSA scans showed no significant change in split function, the improvement does not seem to be due simply to compensatory hypertrophy of the less scarred kidney. We therefore feel that the findings of Helin *et al.* (1975) mentioned above warrant further study in humans.

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Conservative Management of Vesicoureteric Reflux in the Congenital Neurogenic Bladder

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Summary—A series of 31 patients with congenital neurogenic bladder in which vesicoureteric reflux was managed conservatively by methods designed to improve voiding function is reported. Satisfactory results, in terms of the appearance of the upper urinary tracts on IVU, were obtained by indwelling urethral catheter, or by alpha-adrenergic blockade, internal urethrotomy or external urethral sphincterotomy; in the case of the last 3 procedures this was accompanied by diminution or resolution of vesicoureteric reflux. Less satisfactory results were obtained by intermittent self catheterisation and in patients managed in this way a case exists for ureteric reimplantation.

It was once customary to distinguish clearly between primary and secondary vesicoureteric reflux (VUR). While this distinction is not clear-cut, it reminds one that if there is outlet obstruction it requires as much attention as the VUR. It is well established that VUR usually resolves after ablation of posterior urethral valves (Johnston, 1979) and it can also resolve in patients with acquired neurogenic bladder by measures designed to minimise residual urine (Ross, 1965).

VUR is common and is perhaps the major cause of renal morbidity in patients with congenital neurogenic bladder (Light and van Blerk, 1977), yet no consensus exists as to the best means of handling this problem. For several years the prevalent view was that in the presence of the more severe degrees of VUR only permanent urinary diversion could prevent further renal damage (Smith, 1972; Eckstein, 1974; Forrest, 1976). The indifferent long-term results of urinary diversion in children have prompted new policies and currently ureteric reimplantation enjoys some favour, with several centres reporting tolerably satisfactory results (Jeffs *et al.*, 1976; Johnston *et al.*, 1976; Hirsch *et al.*, 1978; Belloli *et al.*, 1979; Kass *et al.*, 1981).

We report the results of a more conservative policy which accepts a relation between bladder outlet obstruction and VUR and concentrates on the former rather than the latter.

Patients and Methods

The series comprised 31 patients with congenital neurogenic bladder (29 with myelomeningocele, one with sacral agenesis and one with a lipoma of the cauda equina) managed by one of the authors (A.M.K.R.) from 1974 to date, and having a total of 40 renal units with VUR grade II in 5 and grade III in 35. Eighteen patients were male and 15 female, and their ages when VUR was first demonstrated ranged from 2 months to 18 years.

Because only a minority underwent full urodynamic assessment prior to treatment, bladder function, where relevant, is simply classified as

Table 1 Systems for Classifying Residual Urine, IVU Appearances and Vesicoureteric Reflux

Residual urine	
Large	>50% of normal bladder capacity
Moderate	20-50% of normal bladder capacity
Small	<20% of normal bladder capacity
IVU	
Grade 0	Normal upper tract
Grade 1	Ureteric distensibility only
Grade 2	Ureteric and pelvicaliceal dilatation—mild
Grade 3	Ureteric and pelvicaliceal dilatation—moderate
Grade 4	Ureteric and pelvicaliceal dilatation—severe
Grade 5	Non-function
VUR	
Grade I	Ureteric only
Grade II	Ureteropelvicaliceal without dilatation
Grade III	Ureteropelvicaliceal with dilatation

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

spontaneous or by expression (or straining). The classification of residual urine, IVU appearances and VUR is described in Table 1.

Management

A. Patients with normal IVU and small residual urine. This group received no treatment for their VUR but were carefully followed up with routine urine sampling, measurements of residual urine and annual IVUs, and infection was treated.

B. Patients with upper tract dilatation on IVU and/or large residual urine. The treatment of this group aimed at eliminating residual urine and/or lowering bladder outlet resistance by one of the following measures:

1. Intermittent self catheterisation (ISC).
2. Permanent indwelling urethral catheterisation (IUC).
3. Alpha-adrenergic blockage (expressible bladders only) using phenoxybenzamine in a daily dose of 0.5 mg/kg.
4. Internal (Otis) urethrotomy (Rickwood, 1982).
5. External urethral sphincterotomy (males only). The procedure was performed transurethrally with a single anteromedian incision of the sphincter (Madersbacher and Scott, 1976), except for one patient who had a transperineal sphincterotomy (Zachary and Lister, 1972).

The choice of treatment was determined by a number of factors, the most important being the patient's sex, age, mobility and intelligence. Although the condition of the upper renal tracts was the prime concern, consideration was always given to achieving continence, with or without an appliance. If the initial line of treatment proved ineffective, another from those listed above was tried.

Results

A. The no-treatment group consisted of 7 cases (4 male, 3 female) with 10 refluxing units. The initial residual urine was small in 6 patients but large in one; this high residual was overlooked and the patient's refluxing upper tract rapidly deteriorated.

In 2 patients the residual urine has remained low over a 2-year period and although VUR persists, the upper tracts remain normal. In 4 cases the refluxing upper tracts have deteriorated and the residual urine increased, and in one of these unilateral VUR became bilateral.

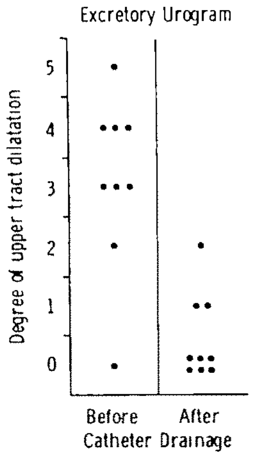
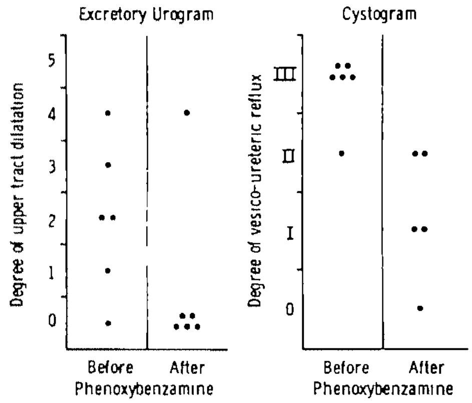


Fig. 1 Degree of upper tract dilatation in 7 patients treated with indwelling catheters. Each point represents the state of an individual refluxing renal unit before and after treatment. Degree of vesicoureteric reflux before catheter drainage: grade III—8 units and grade II—one unit.

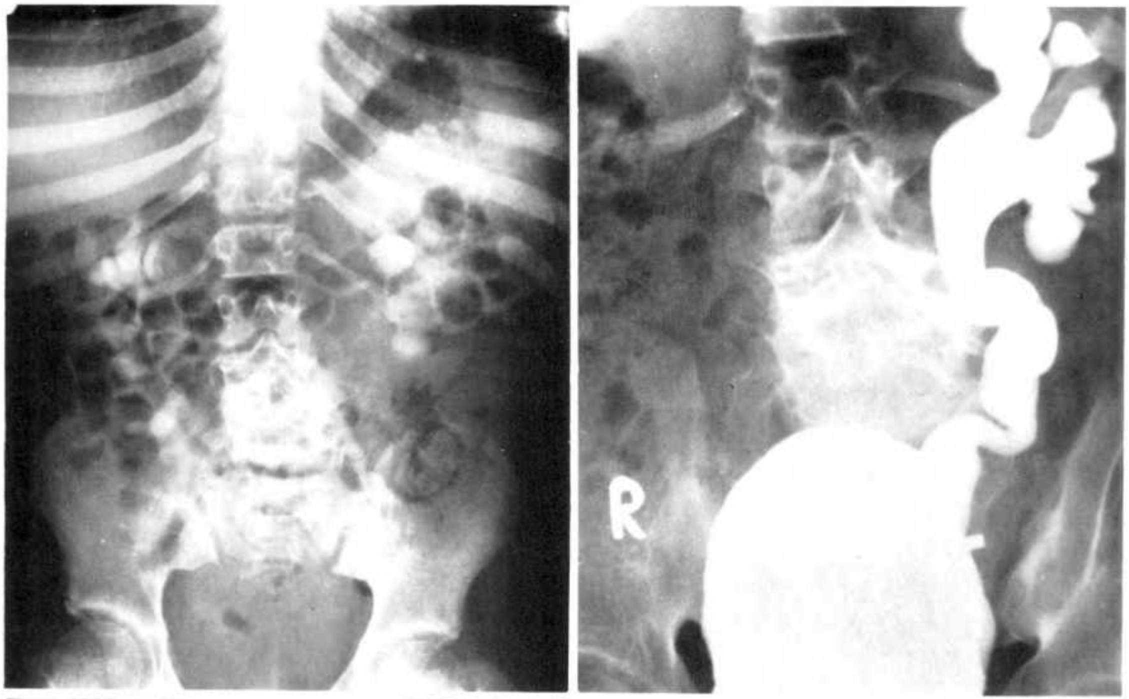
In 5 patients of this group, therefore, the upper tracts have deteriorated. This deterioration has been reversed by external sphincterotomy in 3, by urethrotomy in one and by permanent catheterisation in one.

B. Treatment Group (1) Intermittent self catheterisation—5 cases (3 male, 2 female) with 5 refluxing units. In each case the pre-treatment residual was large. Only one patient continues to be managed solely by ISC because his affected upper tract remains only mildly dilated after 2 years'



(1 patient [1 unit] failure with Phenoxybenzamine - no follow up cystogram done)

Fig. 2 Radiological findings in 5 patients treated with phenoxybenzamine (6 refluxing units).



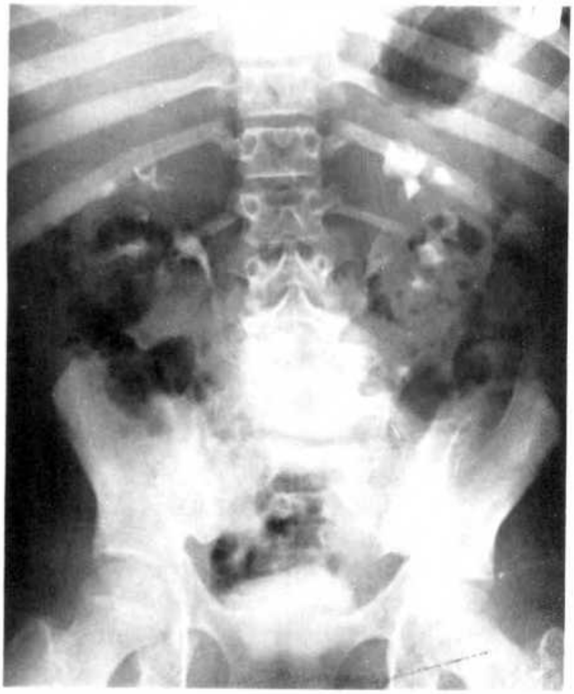


Fig. 3 K.H., female, partial sacral agenesis. (a) (top left) IVU aged 12 years. Right hydronephrosis grade III, left grade IV. (b) (top right) Cystogram aged 12 years. Grade III left VUR. (c) (left) IVU after 8 months' treatment with phenoxybenzamine. Complete resolution of hydronephrosis; residual renal parenchymal damage on the left. (A subsequent cystogram showed grade I left VUR.)

ISC was abandoned in 2 cases, in one because of recurrent urinary infections (later successfully treated by external sphincterotomy) and in the other because a severely dilated upper tract did treatment, though grade III VUR persists. Two patients remain on ISC but their refluxing upper tracts have both markedly deteriorated and VUR has continued; one of these patients has successfully undergone ureteric reimplantation and the other awaits this procedure.

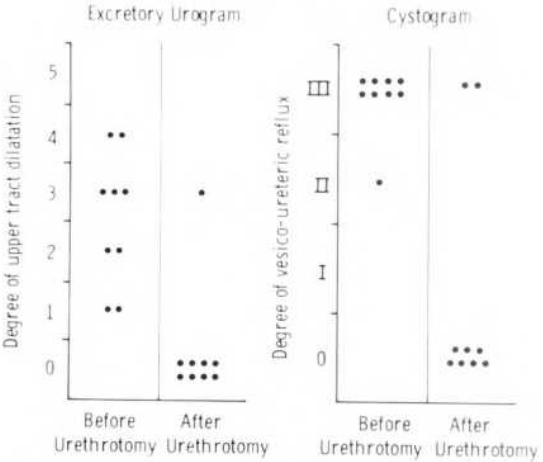
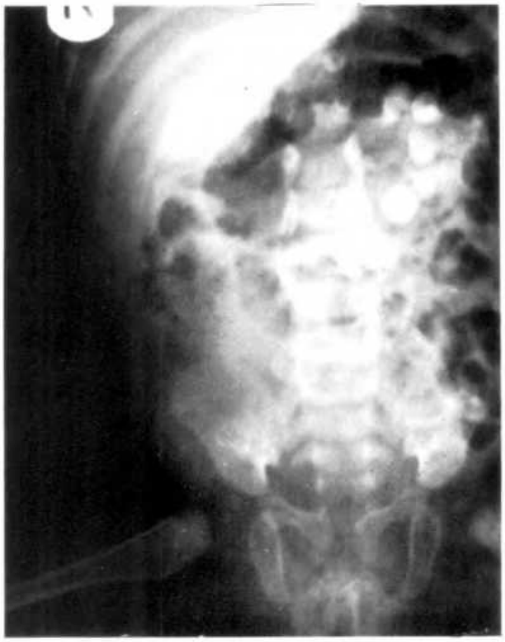
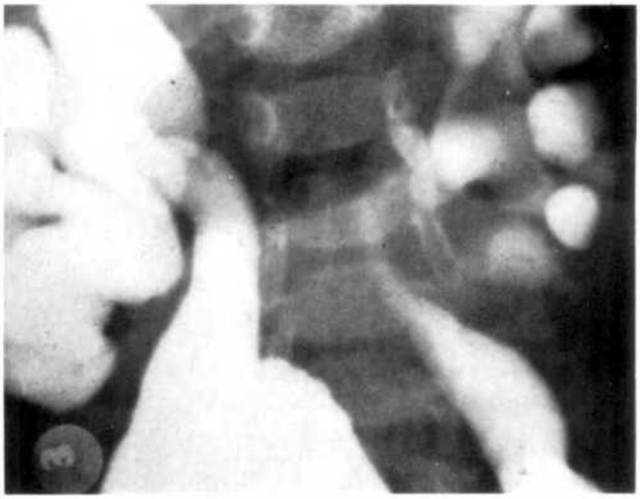


Fig. 4 Radiological findings in 5 patients treated with Otis urethrotomy (9 refluxing units).





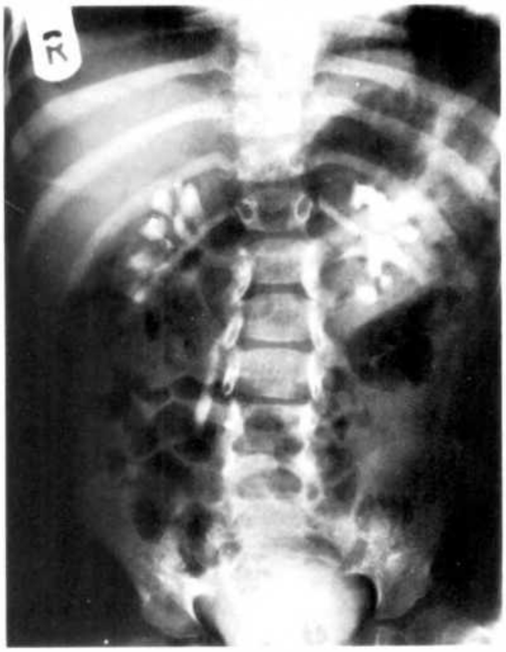


Fig. 5 S.A., female, thoracolumbar myelomeningocele. (a) (top left) IVU aged 5 months. Right hydronephrosis grade IV, left, grade III. (b) (top right) Cystogram aged 5 months. Bilateral grade III VUR. (c) (left) IVU 2 years following internal urethrotomy. Complete resolution of hydronephrosis but residual renal parenchymal damage, more marked on the right. A cystogram showed no VUR.

not improve on this treatment. This patient is now on IUC.

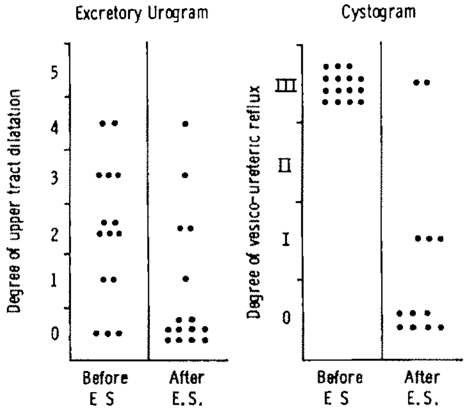
(2) Indwelling urethral catheter (Fig. 1)—7 cases (1 male, 6 female) with 9 refluxing units. It includes 2 patients first treated by other means.

The pre-treatment residual urine was large in 6 patients and small in one who had gross bilateral hydronephrosis. The response, in terms of resolution of upper tract dilatation, has been uniformly satisfactory and in the 5 female patients remaining on this treatment, improvement has been maintained for periods of 2 to 7 years. One female patient, early in the series, later underwent ureteric reimplantation but her upper tracts again deteriorated, necessitating permanent urinary diversion. One male patient, whose massively dilated refluxing upper tract was not improved by sphincterotomy, responded well to IUC, but was later satisfactorily managed with phenoxybenzamine alone.

Because of the excellent response shown by IVU in this group it was not felt necessary or justifiable to perform follow-up cystography to assess the progress of the VUR. Although most patients suffered symptomatic urinary infections before IUC, none have done so since.

(3) Alpha-adrenergic blockade (Fig. 2)—5 cases (3 male, 2 female) with 6 refluxing units. It includes one case previously treated by IUC.

The pre-treatment residual urine was large in 4 patients and small in one. The response has been satisfactory in 4 cases and the residual urine is now small. This improvement has been maintained over periods of 8 months to 4 years. These patients are now dry or only slightly damp on regular expression or straining, whereas 3 were grossly incontinent before treatment. An example of a satisfactory result is shown in Figures 3a, b and c.



No post sphincterotomy cystogram in -
1 patient (1 unit) - Allergic to contrast
1 patient (2 units) - Lost to follow up

Fig. 6 Radiological findings in 13 patients treated with external sphincterotomy (ES) (15 refluxing units).

The one failure in this group retained a large residual urine and her refluxing upper tract further deteriorated; these changes were subsequently reversed by IUC.

(4) Internal urethrotomy (Fig. 4)—5 cases (2 male, 3 female) with 9 refluxing units.

The pre-treatment residual urine was large in 4 and moderate in one case. One patient was aged 10 years; all of the others were less than 2.5 years of age. In the 4 patients with a satisfactory response the residual urine is now small and the improvement has been maintained over periods of 3 to 5 years; an example is shown in Figures 5a, b and c. The 3 female patients were later treated by IUC, 2 purely for incontinence and one who showed no response to urethrotomy.

(5) External sphincterotomy (Fig. 6)—13 cases with 15 refluxing units, including one case previously treated by other means.

The pre-treatment residual urine was large in 11 and moderate in 2 cases. The results can be considered satisfactory in terms of the IVU appearances in 11 cases (with 18 months to 7 years follow-up) and in 9 of these there has been a reduction of residual urine and diminution or resolution of VUR; an example is shown in Figure 7. Information is incomplete in the other 2 because of loss to follow-up in one and allergy to contrast material in the other.

Of the 2 failures, one responded to IUC, and later phenoxybenzamine, while the other underwent ureteric reimplantation.

The overall results are summarised in Table 2.

Table 2 Overall Results for Each Method of Management

	Satisfactory result	*Failure*
No treatment	2	5
Intermittent self-catheterisation	1	4
Indwelling catheter	7	0
Alpha-adrenergic blockade	4	1
Internal urethrotomy	4	1
External sphincterotomy	11	2

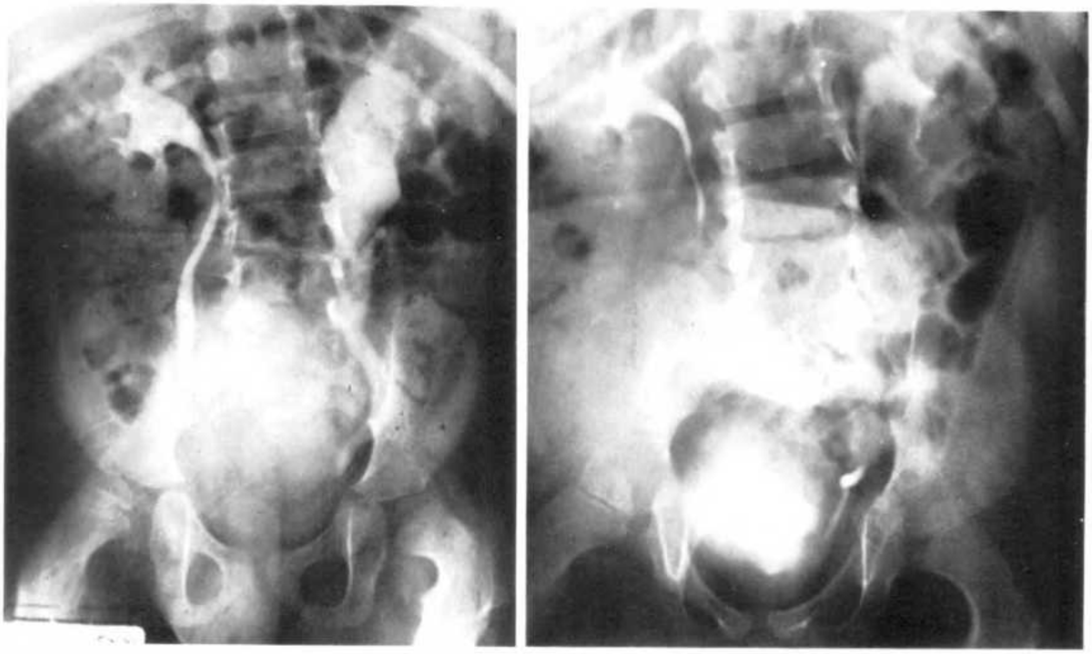
In addition it should be noted that of the renal units treated successfully in terms of resolution of upper tract dilatation, 15 now show some degree of renal parenchymal damage, but 12 of these were severely dilated (grade III or more) before treatment. In no successfully treated case has renal parenchymal damage further progressed.

Discussion

It is our experience that in patients with congenital neurogenic bladder, deterioration of the upper renal tracts, whether there is VUR or not, is almost invariably associated with bladder outlet obstruction. This obstruction is usually revealed by a high residual urine but occasionally, in "reflex" bladders, by high voiding pressures alone due to detrusor-sphincter dyssynergia. It is therefore logical to treat these upper tract problems primarily by methods which improve voiding function, and in the 5 years since this became our routine policy it has never been necessary to resort to urinary diversion to deal with deteriorating upper renal tracts in a patient with spina bifida.

In the presence of VUR, reimplantation may be seen as an alternative to diversion, but it is not without difficulty in a thick-walled, trabeculated neurogenic bladder and may exchange reflux for obstruction (Hirsch *et al.*, 1978). Only some advocates of reimplantation have considered the concomitant problem of bladder outlet obstruction (Jeffs *et al.*, 1976; Johnston *et al.*, 1976; Kass *et al.*, 1981) and few appear to regard it as being of primary importance. This is at odds with the usual practice of treating the obstructed bladder, and surprising in view of the several effective methods now available for improving the voiding function of the neurogenic bladder.

That the results reported here are at least as good as any reported from urinary diversion or ureteric reimplantation suggests that our basic



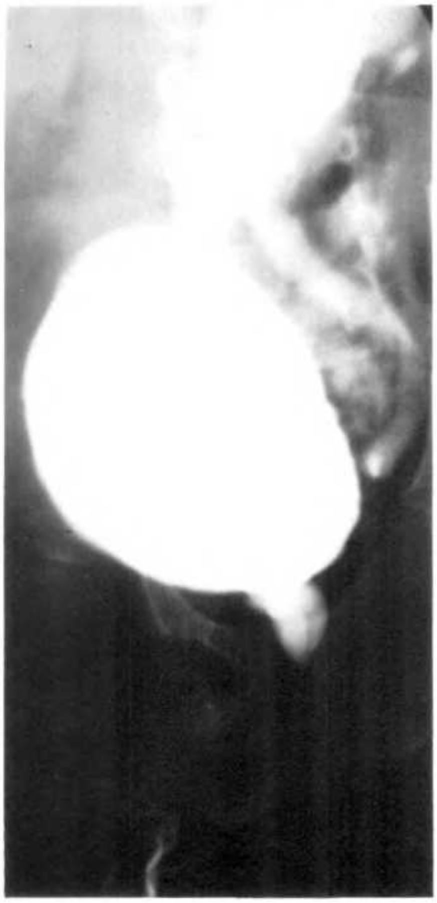


Fig. 7 (a) (top left) IVU aged 6 years. Left hydronephrosis grade III. D.B., male, lumbar myelomeningocele. (b) (top right) Cystogram aged 6 years. Grade III left VUR. (c) (left) IVU 12 months following external urethral sphincterotomy. Complete resolution of hydronephrosis with no residual renal parenchymal damage. A cystogram showed no VUR.

principle of treatment is soundly based but, like other principles, it must be qualified.

(1) An expectant policy in the presence of grade II or III VUR is hazardous and justified only when outlet obstruction has been positively excluded. Whenever there is any element of outlet obstruction, active intervention is advisable even though the IVU appearances may be normal.

(2) When there is grade III VUR, the results of ISC are poor, and our small series confirms the findings of others (Kass *et al.*, 1981). The intention to use ISC in the treatment of the congenital neurogenic bladder with VUR seems to be the principal indication for ureteric reimplantation in those patients.

(3) Alpha-adrenergic blocking agents usually reduce residual urine only in patients with an expressible or strainable bladder (Hachen, 1980) and they do not influence residual urine resulting from detrusor-sphincter dyssynergia. Even when effective, we would regard their use as justified only when continence is also improved. If it is not, some other means of improving bladder emptying seems preferable to long-continued medication.

(4) There is some evidence that internal urethro-

tomy is effective mainly in young patients (Rickwood, 1982) and its use is best limited to infant females for whom IUC may later be the most effective means of securing dryness.

(5) For boys, division of the external sphincter must be deep for it to be effective. For some years it was the practice in Sheffield to perform an open, transperineal sphincterotomy (Zachary and Lister, 1972). The results were less than ideal, and transurethral antero-median sphincterotomy has given consistently satisfactory results in our hands.

(6) Procedures such as urethrotomy and external sphincterotomy can, and sometimes do, reduce the bladder capacity, which precludes the use of ISC. To be successful, ISC requires not only a bladder of sufficient capacity, but also a patient with adequate mobility, manipulative skill and motivation, and these are commonly lacking in the more severely affected patients with myelomeningocele. For them the only realistic means of securing dryness is an indwelling catheter for girls or a penile urinal for boys.

(7) Although IUC is a highly effective means of reversing upper tract dilatation, its effect on VUR is unknown. However, our experience of this form of management suggests that, in practice, whether VUR resolves or not is immaterial. We have confined IUC almost exclusively to females because it can cause urethral complications in boys.

Worldwide experience in the last 2 decades has shown only too clearly the prevalence of upper renal tract problems and VUR in patients with congenital nuerogenic bladder, even in those whose physical disabilities are otherwise slight or non-existent. For most of that period it has also seemed that the means of tackling these problems, principally by urinary diversion, were unequal to the task. While there are now grounds for optimism, it would be idle to pretend that all difficulties have been solved and the methods of management advocated in recent years have yet to stand the test of time. However, we believe that the application of basic principles goes some way towards solving the problems of VUR in the congenital neurogenic bladder without major surgery.

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Bladder Transection—a Functional, Neurophysiological, Neuropharmacological and Neuroanatomical Study

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Summary—Experimental models to represent the surgical methods of bladder transection in humans were performed on dogs and rabbits. The effects on vesical neurophysiology were studied by cystometry with bethanechol supersensitivity testing; by *in vitro* pharmacological responsiveness; by determination of autonomic receptor densities using radioligand binding and by autonomic neurohistochemical staining. Analysis revealed that transection with or without neurovascular preservation resulted in an alpha-adrenergic denervation and cholinergic decentralisation. A comparison with the surgical models is presented and proposed mechanisms of action are discussed in relation to the experimental results.

The use of bladder transection, with division of the inferior lateral connections, was introduced for the control of uninhibited bladder contractions by Turner-Warwick and Ashken (1967). A modified procedure employing transection alone was reported by Yeates (1970) and additional reports by Essenhigh and Yeates (1973), Gibbon *et al.* (1973), Hindmarsh *et al.* (1977), Parsons *et al.* (1977), Janknegt *et al.* (1979) and Mundy (1980) have so far reported 123 patients, with improvement in approximately 75%. Although bladder denervation has been proposed as an explanation for the improvement in symptoms, urodynamic testing and experimental studies have done little to substantiate this as the reason for the beneficial effect.

The present study was performed to investigate the effects at the neural and muscular level of the operations proposed for the treatment of the urgency incontinence syndromes.

Materials and Methods

Eight male New Zealand white rabbits had bladder transections (Fig. 1b) by the following method. The bladder was exposed through a midline incision and after dissection of the superior vesical artery mesentery from the bladder body, complete transection with vascular preservation was performed above the level of the ureteric orifices. Control biopsies were taken from the ventral aspect of the bladder body, a drainage catheter placed *per urethram* and the bladder closed in a single layer. The urethral catheter was removed on day 2 and the rabbits were sacrificed on day 14 (2), day 40 (4) and day 120 (2) for analysis.

Eleven female beagle dogs (15-20 kg) were lightly sedated with pentobarbital (IV) and catheterised *per urethram* (14 FG Foley). A cystometrogram and bethanechol supersensitivity test (0.03 mg/kg Urecholine) was recorded on each dog. The bladder was exposed through a midline incision and 1 of 4 surgical options performed (Fig. 1).

(*a*) Cystograft—division of the bladder above the level of the ureteric orifices without vascular preservation.
(*b*) Transection—division of the bladder above the level of the ureteric orifices with vascular preservation to the fundus.
(*c*) Peripheral denervation—division of the inferior neurovascular pedicles.
(*d*) Transection with peripheral denervation—(*b*) and (*c*) above.

Biopsy specimens from the ventral bladder body were taken, a urethral catheter inserted and the bladder body closed in a single layer. The catheter was removed on the seventh post-operative day and the bladders were rebiopsied on days 40 and 120. Further cystometrographic analysis was performed before each re-exploration.

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

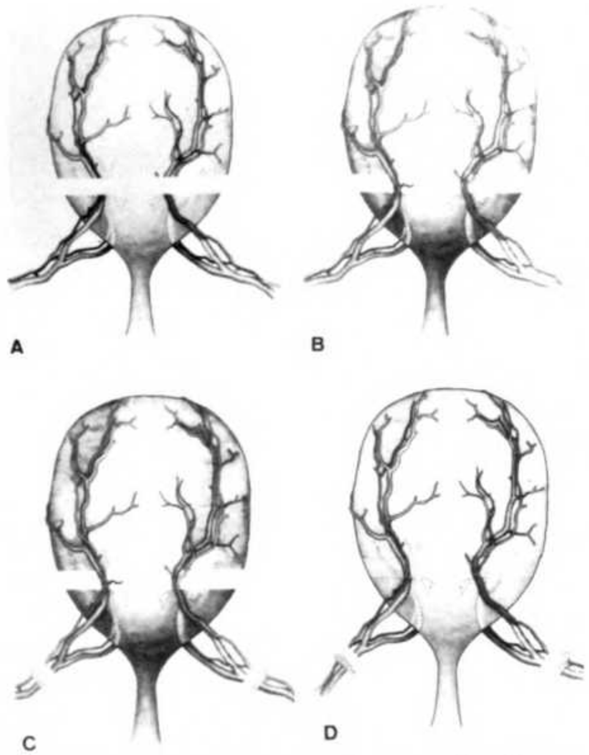

Fig. 1 Experimental models of bladder transection: (a) cystograft; (b) transection; (c) transection with peripheral denervation; (d) peripheral denervation.

Muscle Bath Studies

Standard sized (5 × 10 mm) detrusor specimens were orientated and suspended at 1 g tension in Tyrodes solution (with 1 mg/ml glucose added) perfused with 95% O_2 and 5% CO_2 mixture. After equilibration, sequential cumulative dose response curves to bethanechol chloride were performed at 5-min intervals to a maximum dose of 1 mmol.

Receptor Binding Studies

Specimens were immediately frozen in liquid nitrogen. Adrenergic alpha and beta receptor and cholinergic muscarinic receptor densities were determined by standard radio-ligand techniques as described previously (Levin and Wein, 1979), using ^{3}H-Dihydroalprenolol (beta), ^{3}H-Dihydroergocryptine (alpha) and ^{3}H Quinuclidynal Benzilate (muscarinic). Protein was determined by the method of Lowry *et al.* (1951).

Histological Studies

Specimens were immediately frozen in isopentane pre-cooled in liquid nitrogen. Tissue specimens were stained for catecholamines by the glyoxylic acid method of histofluoresence (De La Torre and Surgeon, 1976) and for cholinergic innervation using specific anticholinesterase staining (Koelle, 1955).

Results

Cystometry with In Vivo *Supersensitivity Testing* (Post-operative)

Bethanechol supersensitivity testing yielded a positive response in 2/2 cystografts, 3/5 transections, 2/2 transection with denervations and 1/2 peripheral denervations. Control dogs were positive in 2/11 cases.

Bladder capacity decreased by an average of 27.1 ± 11.9% in all groups. There were no significant differences among the 4 groups.

Muscle Bath Studies (In Vitro Pharmacological Response)

The bethanechol induced contractile response seen in the controls was significantly decreased in specimens taken at 40 days (Fig. 2). The response at 120 days returned towards normal levels in the dogs. In rabbits, the response at 14 and 40 days did not differ significantly from the control responses but at 120 days a supersensitive response was recorded (Fig. 3).

Autonomic Receptor Densities

Autonomic receptor densities were measured on transection and transection with peripheral denervation specimens. The effect of transection on the receptor density of the canine bladder is shown

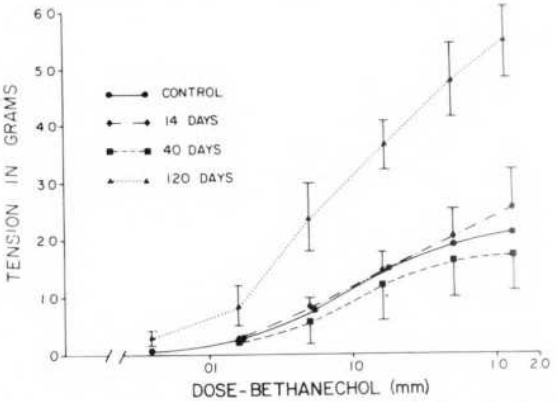

Fig. 2 *In vitro* dose response curves to bethanechol after bladder transection (dog).

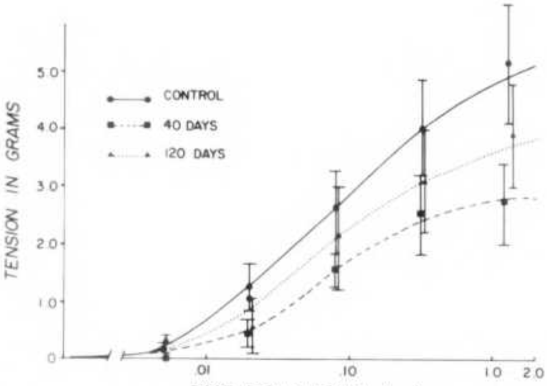

Fig. 3 *In vitro* dose response curves to bethanechol after bladder transection (rabbit).

in Figure 4. At 40 days following transection there were significant increases in both muscarinic cholinergic and alpha-adrenergic receptors. The beta-adrenergic receptor density was unchanged by transection.

The receptor densities in dogs that had transection with peripheral denervation are shown in Figure 5. As observed in the transection alone, there were increases in both alpha-adrenergic and muscarinic cholinergic receptors, whereas the beta-adrenergic receptor density did not change.

Autonomic Neurohistochemical Testing

Analysis and grading of histological specimens was performed in a single-blind fashion.

Cholinergic neurohistology All of the surgical groups showed persistence of cholinergic ganglia, neurones and nerve fibre innervation of the bladder dome. Cystograft and transection with peripheral denervation specimens had a moderate quantitative decrease in cholinergic innervation when compared with the control biopsies. The density of cholinergic innervation in the transection and the peripheral denervation specimens was minimally reduced (Figs. 6 and 7). All post-

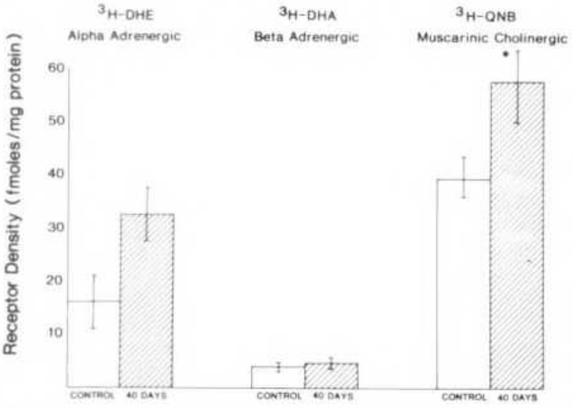

Fig. 4 Radioligand binding before and after transection (dog).

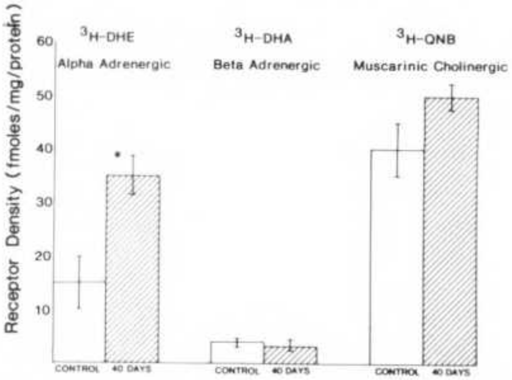

Fig. 5 Radioligand binding before and after transection with peripheral denervation (dog).

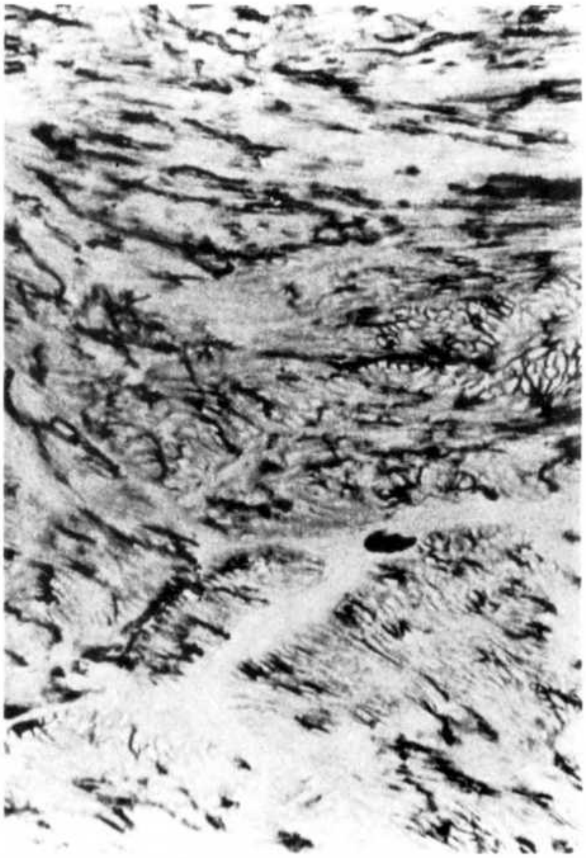

Fig. 6 Control cholinergic innervation of dog bladder (×120).

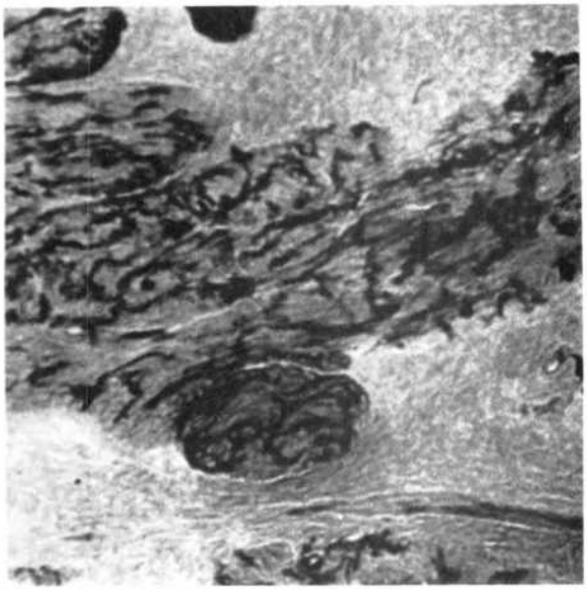

Fig. 7 Post-transection cholinergic innervation of dog bladder—note increased collagen (× 120).

operative specimens had increased collagen deposition.

Analysis of specimens from rabbit transection models at 14, 40 and 120 days showed results consistent with the canine cholinergic histology.

Adrenergic Neurohistology The cystograft, transection and transection with denervation specimens revealed a significant decrease in sympathetic nerve distribution and density when compared with controls (Figs. 8 and 9). In most specimens adrenergic nerves were seen only in association with the vasculature and were completely absent from muscle fibres. Specimens from dogs with peripheral denervation showed persistence of adrenergic innervation of the musculature.

The rabbit transection model was consistent with the canine findings. At 120 days, adrenergic nerve "sprouting" into the muscle from blood vessels was noted.

Discussion

The severe impact of the disabling symptoms associated with adult enuresis, urgency and urge incontinence have prompted the use of surgical procedures for those patients refractory to behavioural or drug therapy. Supratrigonal full thickness bladder transection appears to be one of the most promising surgical methods in the management of the unstable bladder syndromes. Peripheral denervation, alone or in combination with transection, has also been advocated.

The post-operative improvement in symptoms produced by each of these surgical methods has been assumed to be due to bladder denervation. This study used several different methods to analyse the degree of denervation of the bladder that occurred in experimental models which matched the "denervation" procedures used in humans.

Bethanechol supersensitivity testing is an accepted clinical method to diagnose cholinergic denervation of the bladder. The conversion to positive of the majority of dogs tested in this experiment implies a degree of post-operative denervation in some animals. The observed decrease in absolute bladder capacity under general anaesthesia should not be confused with the subjective clinical responses noted in humans where a cystometric shift to the right was found, with an increase in mean voided volume.

The *in vitro* response to bethanechol of rabbit

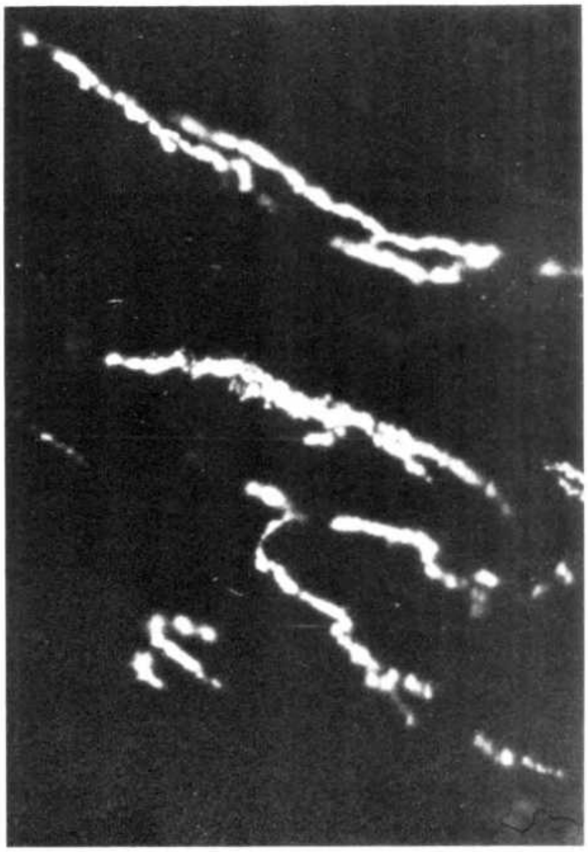

Fig. 8 Control adrenergic innervation of dog bladder (fluorescent photomicrograph × 250).

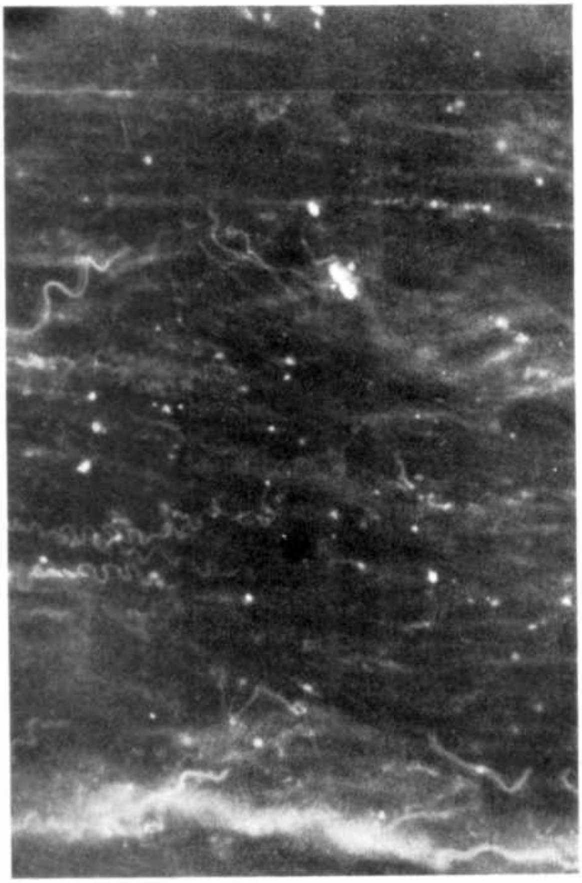

Fig. 9 Post-transection adrenergic innervation of dog bladder (fluorescent photomicrograph ×250).

bladder muscle, tending to confirm that significant denervation had occurred, was shown by an exaggerated contractile response at 120 days. The dog data, on the other hand, did not support this conclusion, presumably because the increase in collagen deposition hindered contractility.

Muscle membrane receptors for neurotransmitters have been shown to proliferate as a result of denervation. Measurement of absolute receptor numbers by radio-ligand binding therefore permits an alternative assessment of denervation. The finding that the transection and transection with peripheral denervation models induced an increase in the muscarinic cholinergic and alpha-adrenergic receptor densities would indicate that muscle fibres of these 2 systems were devoid of neuronal continuity.

The conclusion of these pharmacological methods of analysis supports the hypothesis that bladder transection produces a degree of denervation. However, the extent to which decentralisation of intramural cholinergic ganglia contributes to cholinergic receptor proliferation, resulting in the observed effects, is undetermined. Study of the neuronal architecture of the bladder by neurohistochemical techniques has helped to clarify the distinction between denervation and decentralisation. Reference to each of the transection models in this experiment allows more precise conclusions regarding the level of neuronal disruption.

The cystograft model was unique in that neural or vascular sparing above the line of vesical division could not occur. The presence of cholinergic ganglia and nerves and the absence of sympathetic innervation demonstrated that (1) cholinergic innervation is dependent upon the presence of ganglia in the fundus and that these ganglia are surgically decentralised by transection; (2) quantitative changes in nerve supply were secondary to disappearance of neurones whose ganglia were below the line of division; (3) sympathetic denervation occurred because of interruption of sympathetic neurones as sympathetic ganglia at the fundus were absent. No proliferation of nerves through the surgical scar was seen.

Transection with vascular preservation resulted in decentralisation of fundal ganglia but showed minimal change in cholinergic innervation. Sympathetic denervation was also noted. This demonstrates that (1) vascular preservation resulted in a degree of cholinergic but not sympathetic nerve sparing; (2) sympathetic nerves to muscle fibres traverse the bladder intramurally from base to fundus and are not associated with the major fundal vasculature, and are interrupted by bladder division.

In those experiments where peripheral denervation was undertaken, despite extensive inferolateral dissection, cholinergic innervation was only minimally changed and sympathetic innervation persisted. This implies that sympathetic neural sparing occurred and that the degree of decentralisation or denervation was dependent on whether pre- or post-ganglionic neurons were divided. In the majority of specimens, the persistence of cholinergic ganglia indicated that only pre-ganglionic neurons were affected.

The results of this study confirm that bladder transection has the potential to alter significantly bladder function predominantly in the storage phase. An alteration in the neural supply to the detrusor above the line of division occurs, but without causing major cholinergic denervation as judged by neurohistology.

Bladder transection offers an added effect by interruption of the detrusor syncytium, affecting intramural smooth muscle conduction pathways, interneurones and the mechanical function of the fibres and fibre network by surgical disruption or secondary to post-operative fibrosis. Further detrusor myotomies would theoretically be expected to increase the ratio of denervated to decentralised areas.

Bladder division methods (Figs. 1a, b and c) result in alpha-adrenergic denervation of the fundus, while peripheral denervation alone (Fig. 1c) permits persistence of sympathetic neurones.

The multifactorial effects of the alpha-sympathetic system by a direct effect on muscle tone, or through an inhibitory influence on cholinergic ganglia, lead to the proposition that sympathetic denervation could produce a facilitatory or an inhibitory effect. Alpha receptor proliferation at cholinergic ganglia in response to denervation may enhance inhibition and therefore be beneficial in facilitating bladder storage.

Acknowledgements

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Addendum

Based on these experimental findings it was realised that the same effects of alpha-adrenergic denervation of the fundus, and interruption of the myoelectrical and intrinsic neuronal element of the detrusor syncytium, could be achieved in humans by endoscopic transection of the bladder. This procedure has been introduced in Portsmouth to see whether the beneficial effects of the open operation can be matched by this less radical approach. A series of endoscopic transections is currently in progress.

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A Prospective Study of Bladder Function Before and After Sphincter-saving Resections for Low Carcinoma of the Rectum

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Summary—The effects of sphincter-saving resections for carcinoma of the rectum on bladder function were studied prospectively. Twenty-seven patients, each acting as his or her own control, were studied before, shortly after and 9 months after operation by means of pressure/flow filling and voiding cystometry.

After operation there was a significant and lasting increase in the residual volume of urine and a temporary decrease in the compliance of the bladder. There was a statistically significant decrease in detrusor contraction pressure after operation, which persisted throughout the period of study. This was probably due to partial denervation of the bladder. Four patients had signs of total or almost total denervation of the bladder. There was a significant correlation between proximity of the tumour to the anal verge and risk of damage to the nerve supply to the bladder.

Thus sphincter-saving resections of the rectum for carcinoma are associated with a significant risk of bladder denervation. Many of the "minor" symptoms of bladder dysfunction which develop after this procedure are due to partial denervation of the bladder.

Recent modifications of operative techniques, such as per-anal colo-anal anastomosis (Parks, 1972) and use of the mechanical stapling device (Goligher, 1979), have encouraged more surgeons to perform sphincter-saving resections for tumours in the lower part of the rectum. The majority of patients eventually regain continence after such procedures (Lane and Parks, 1977; Williams *et al.*, 1980a). Denervation of the bladder is not uncommon after abdomino-perineal excision of the rectum for carcinoma (Rankin, 1969; Fowler *et al.*, 1978) and, in contrast to some earlier reports (Rankin, 1969), bladder dysfunction has also been noted after sphincter-saving resection (Goligher, 1975; Williams *et al.*, 1980b; Kirkegaard *et al.*, 1981).

Prospective studies, using each patient as his or her own control, are needed if an accurate picture of the effects of rectal excision on bladder function is to be obtained. In particular, patients should be allowed several months before they are re-tested after operation both to recover from the trauma of surgery and because recovery of autonomic nerve function is a well recognised phenomenon, seen particularly after sympathectomy and vagotomy.

Patients and Methods

Twenty-seven patients (14 men, 13 women) with rectal carcinoma whose distal margin was 9±2 cm from the anal margin were studied before, 10 days after (10±3 days) and again 9 months after operation ($\bar{\chi}=9\pm3$ months; range = 3-18 months). Each patient gave informed consent to the study. Other details of the patients, including their age, the precise type of operation performed and the pathological staging of the tumour are shown in Table 1.

Symptoms

Symptoms of bladder dysfunction were assessed by means of a detailed questionnaire completed before and 9 months after operation.

Cystometry

Cystometry was carried out with a Lectromed MX6 pen recorder and Bell and Howell transducers. All definitions used are those recom-

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Details of 27 Patients With Rectal Cancer

Men	14
Women	13
Height of tumour from anal verge ($\bar{x}$±S.D.)	9±2 cm
Age ($\bar{x}$±S.D.)	68.6±10 years
A. Colo-anal anastomosis	7
B. Anterior resection (hand anastomosis)	10
C. Anterior resection with stapling gun	10
Dukes grade A	4
Dukes grade B	11
Dukes grade C_1	8
Dukes grade C_2	4

mended by the International Continence Society (Bates *et al.*, 1979). The residual volume of urine after micturition was first determined. The bladder was then filled through an 8 FG catheter at a medium filling rate (1 ml/s). Intravesical pressure was monitored through a fine epidural catheter and true detrusor pressure was determined by automatically subtracting intra-abdominal pressure, which was estimated by means of a small balloon in the rectum. Compliance was calculated by dividing the maximum capacity of the bladder (measured in ml) by the amount by which the pressure in the bladder increased during filling (measured in cm H_2O). After the filling catheter had been removed the patient voided and detrusor contraction pressure and peak flow rate were recorded. The carbachol test was used to confirm denervation if the post-operative cystometrogram was abnormal (Glahn, 1970a).

Statistical Analysis

The statistical significance of any difference was assessed by means of the Wilcoxon Test for paired data. The Binomial Test was used to assess changes in frequency (Siegal, 1956). Correlation was assessed by means of Kendall's Tau which does not assume that the data are normally distributed.

Table 2 Results of the Symptomatic Assessment

	Before operation	*After operation*	*Significance of difference*
Total with symptoms	9	16	<0.02
Poor stream	4	11	<0.02
Nocturia (>×2)	4	9	<0.06
Sensation of incomplete emptying	0	8	<0.008
Straining during micturition	0	7	<0.016
Urge	1	1	
Nocturnal	0	1	
Incontinence			
Stress	2	4	N.S.
After micturition	2	4	

Table 3 Results Derived From Cystometry

	Pre-operative	*Post-operative (10 days)*	*Post-operative (9 months)*
Residual volume (ml)	26±30	115±121†	83±92†
Bladder capacity (ml)	401±157	424±220	447±241
Compliance (ml/cm)	84±46	59±36†	72±52
Detrusor contraction pressure (Men; cm H_2O)	62±21	42±23†	44±18*
Detrusor contraction pressure (Women, cm H_2O)	25±6	16±9*	17±9*
Peak flow rate (men; ml/s)	13±4	10±5*	12±4
Peak flow rate (women; ml/s)	21±4	17±6	18±7

Expressed as means ± standard deviation (n = 27)
* $P < 0.05$; † $P < 0.025$ (compared with pre-operative).
Compliance is expressed in ml/cm H_2O

Results

Subjective Data

Nine patients had symptoms of bladder dysfunction before operation (Table 2). Five were men with symptoms suggestive of prostatism and a sixth man, who had urge incontinence, was later found to have detrusor instability. Two women had stress incontinence. The ninth patient stated that in the weeks preceding his operation he was able to pass urine only when he defaecated; this symptom improved, however, after operation.

After operation a further 8 patients developed symptoms of bladder dysfunction which persisted throughout the test period ($P < 0.02$). A sensation of having a poor stream ($P < 0.02$), having to strain with micturition ($P < 0.02$) or incomplete emptying of the bladder after micturition ($P < 0.01$) were found to be significantly more frequent after operation.

Objective Data (Table 3)

All Patients The residual volume of urine increased significantly immediately after operation (Fig. 1, $P < 0.01$) and although it was found to diminish in the course of the ensuing months, it was still significantly greater than before operation ($P < 0.02$). Immediately after operation the

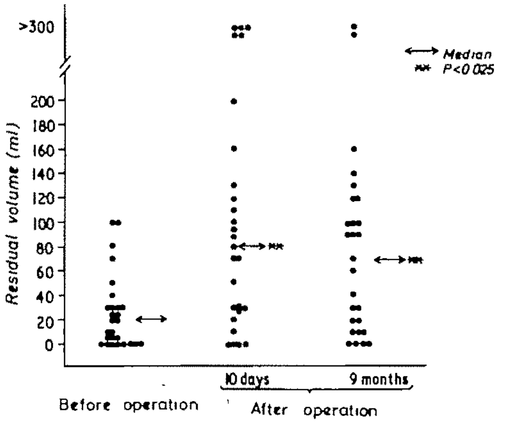

Fig. 1 Residual volumes of urine after micturition, before and after operation

compliance of the bladder decreased significantly ($P < 0.01$), reflecting an increase in the amount by which the pressure in the bladder rose during filling. This decrease in compliance appeared to be temporary, because 9 months after operation compliance was not significantly different from before operation (Fig. 2). Detrusor contraction pressure decreased significantly soon after operation (men, $P < 0.025$; women $P < 0.05$) (Figs. 3 and 4). Nine months after operation, detrusor contraction pressure had increased slightly compared with soon after operation, but was still significantly less than before operation ($P < 0.05$).

A significant inverse correlation was found between the height of the tumour from the anal verge and the amount by which detrusor contraction pressure was reduced, expressed as a percentage of the pre-operative value (Tau = 0.346; $P < 0.02$) (Fig. 5).

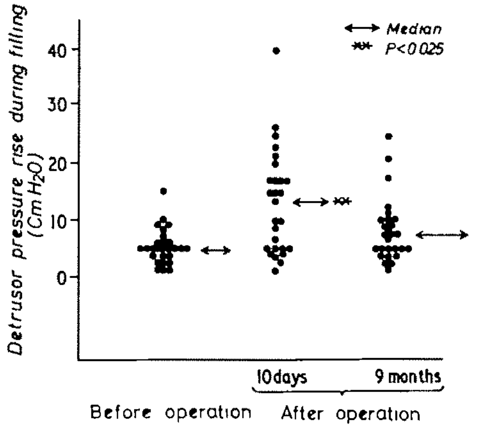

Fig. 2 Detrusor pressure increase during the filling part of cystometry before and after operation.

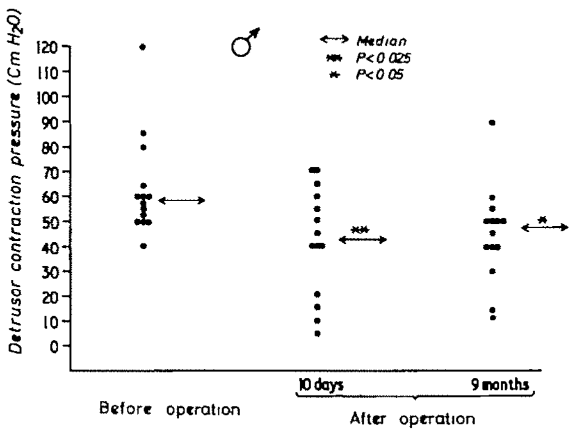

Fig. 3 Detrusor contraction pressure in male patients before and after operation.

Whilst significant changes were found in the group as a whole, 7 patients had more marked changes.

Denervation of the Bladder

Four patients, 2 men and 2 women, had marked dysfunction of the bladder after operation that was characterised by the following features; chronic, painless retention of urine, loss of the normal sensation during bladder filling and near-total loss of detrusor contraction pressure (from a mean of 48±27 cm H_2O before operation to 3±5 cm H_2O after operation). In addition, a reduction in compliance due to a hypertonic filling phase was found in all 4 patients (mean pressure rise = 5±2 cm H_2O before, to 25.5±10 cm H_2O after, operation).

These 4 patients were treated conservatively by means of catheterisation and cholinergic drugs

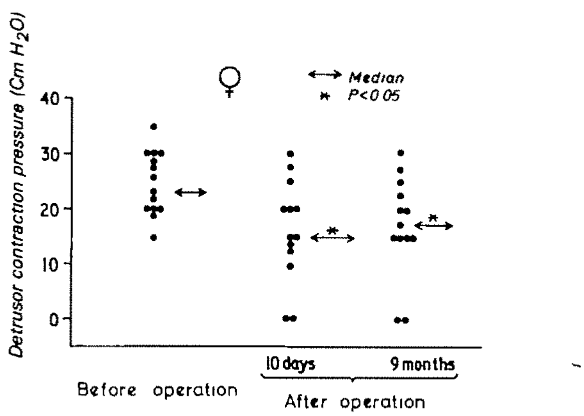

Fig. 4 Detrusor contraction pressure in female patients before and after operation.

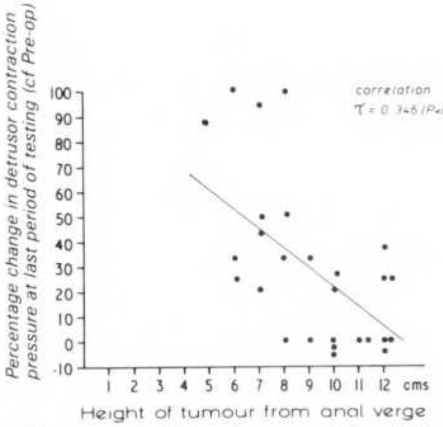

Fig. 5 Diagram correlating the amount by which detrusor contraction pressure was reduced with the height of the tumour from the anal verge.

and were eventually able to void. Nine months after operation, however, all still had symptoms of a poor stream, having to strain and a sensation of incomplete emptying after micturition. One man was impotent and also incontinent occasionally and one of the women had severe nocturnal incontinence.

These findings remained abnormal throughout the period of testing, with high residual volumes (mean = 6.2 ± 2 ml before and 185 ± 152 ml after operation) (Fig. 6) and little recovery of detrusor contraction pressure (mean = 6 ± 6 cm H_2O). Nine months after operation, all had a positive carbachol test but only the 2 men had a hypertonic filling phase of more than 20 cm H_2O during filling. The 2 women had large capacity bladders with an atonic filling phase (mean capacity 625 ± 140 before and 910 ± 14 after operation). Each of these patients had low rectal tumours, the lower margin of which was 7 ± 2 cm from the anal verge on average. Two of them had developed pelvic sepsis after operation due to an anastomotic dehiscence.

Retention of Urine

Apart from these 4 patients, 3 other men developed retention of urine after operation. Two of them had evidence of partial denervation of the bladder, with a reduction in detrusor contraction pressure of more than 30% compared with before operation (Fig. 7). One of these patients had a transurethral resection of the bladder outlet and

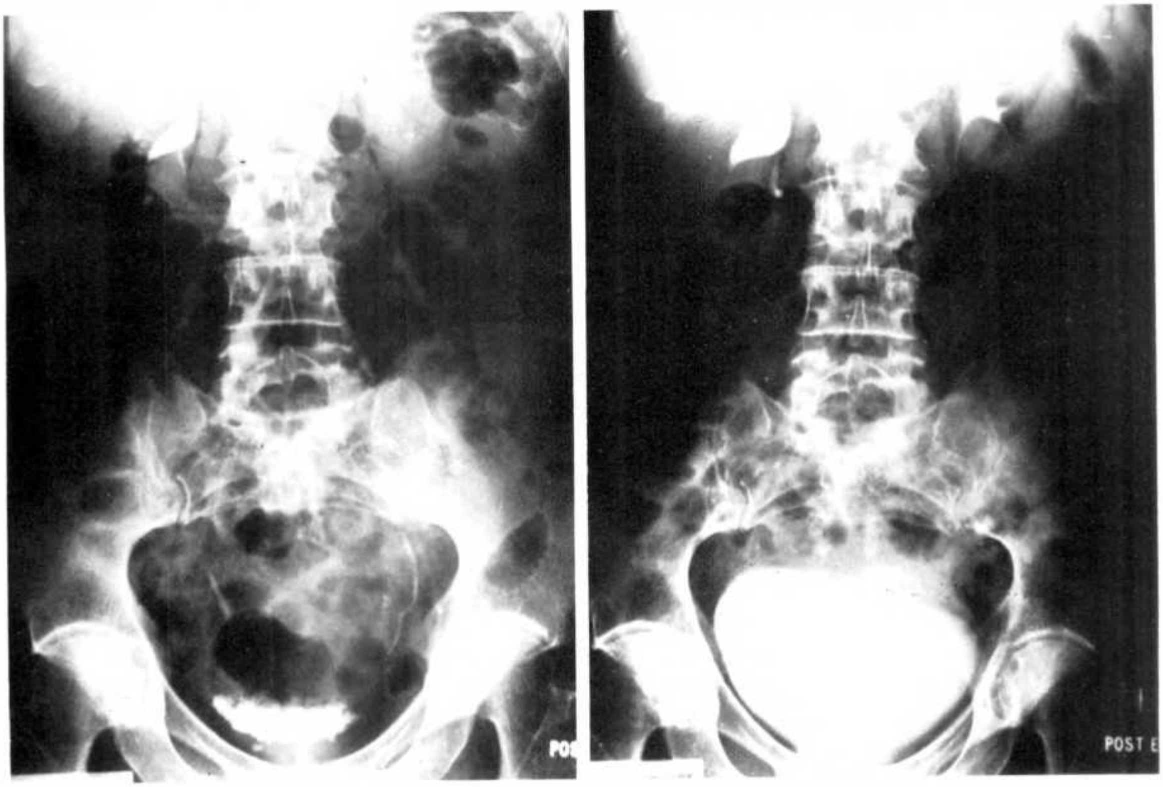

Fig. 6 The post-micturition IVU of one of the female patients who suffered total denervation of the bladder (a) before operation; (b) 3 months after operation.

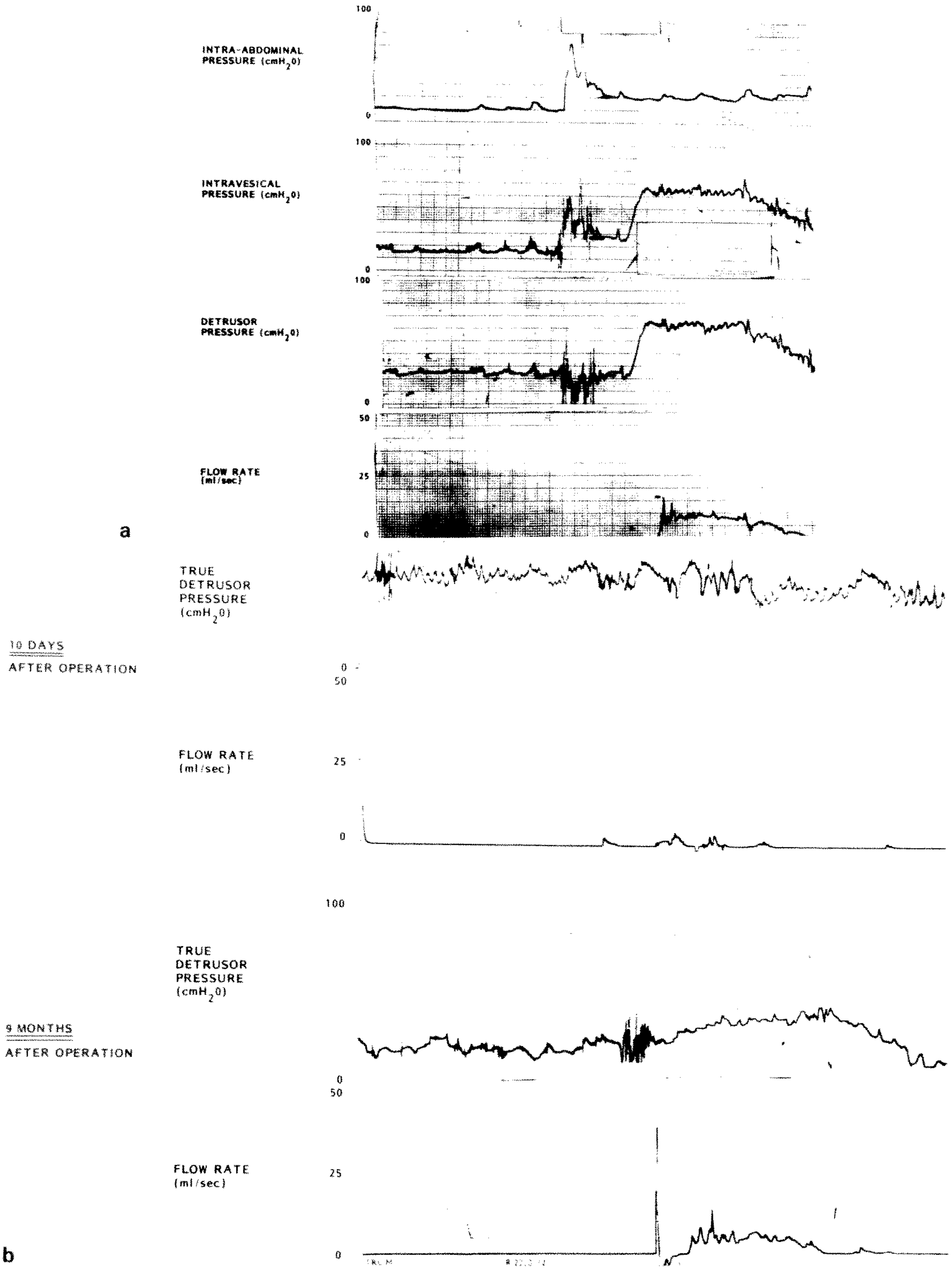

Fig. 7 Voiding cystometrogram of one of the male patients (a) before operation and (b) 10 days and 9 months after operation.

the other was treated conservatively. Their voiding pressures remained low throughout the test period. The other man, who developed acute retention of urine after operation, was treated by transurethral resection of the prostate. This man initially had a hypertonic filling phase to his cystometrogram but 9 months later he had normal filling and voiding studies.

Apart from these 7 patients, one man developed a colovesical fistula secondary to an anastomotic dehiscence and a further man who developed transient detrusor instability also had minor pelvic sepsis.

Discussion

The main findings of this study were that bladder dysfunction was a significant problem after sphincter-saving resections for carcinoma of the rectum and that there was a spectrum of disability due to varying degrees of denervation of the bladder.

It was confirmed that there was a high incidence of urinary symptoms in patients with rectal carcinoma before operation (Peel *et al.*, 1980) and for this reason a prospective study is the only reliable way to assess these patients (Gerstenberg *et al.*, 1980).

The incidence of near-total denervation of the bladder found in this study was 15% (4 of 27 patients). This figure should be compared with previous reported incidences of bladder denervation of 8% (Gerstenberg *et al.*, 1980) 25% (Rankin, 1969) and 50% (Fowler *et al.*, 1978, Eickenberg *et al.*, 1976). The wide variation in the reported incidences of this complication is presumably accounted for by the retrospective nature of some of these studies and the different criteria of denervation that were used. We have used the absence of any co-ordinated detrusor contraction as our basic criterion of denervation (Langley and Anderson, 1896; Murnaghan *et al.*, 1979). Although anxiety may result in an individual being unable to void in the test situation, it is unlikely that in our patients, who had a normal pre-operative study, such psychic factors played a major role. Our findings confirm previous reports of a hypertonic filling phase in some patients with denervation of the bladder (Denny-Brown and Robertson, 1933; Fowler, 1973) but 2 of our patients developed an atonic bladder after initially having a hypertonic type of bladder. This observation, taken in conjunction with the temporary fall in compliance seen in our patients as a whole, provides support for the views of those authors who state that infection, secondary to denervation or the presence of a catheter, is responsible for much of the apparent hypertonia which is seen in these patients (Plum and Colfelt, 1960; Glahn, 1970b).

Many of these patients who have bladder dysfunction after excision of the rectum do not fulfil our criteria for complete denervation. Displacement of the bladder backwards or muscular incoordination of the pelvic floor (Kontturi *et al.*, 1974) is unlikely to be a cause of this problem in our patients, in whom the rectum was replaced by colon and the integrity of the pelvic floor was not compromised. Our data do not allow us to confirm or refute the suggestion that perivesical fibrosis and oedema impair the action of the detrusor muscle (Campbell and Gliason, 1950).

Detrusor contraction pressure is statistically reproducible for any given patient (von Garrelts, 1957; Zinner and Paquin, 1963) and our finding of a significant decrease in this parameter supports previous suggestions that partial denervation is responsible for many of the symptoms of bladder dysfunction seen after excision of the rectum (Eickenberg *et al.*, 1976). Certainly the autonomic nerves may be damaged during rectal excision (Simmons, 1938; Williams and Slack, 1980). The only previous study which measured detrusor contraction pressures in the long term found that, in men after abdomino-perineal excision of the rectum, there was a decrease in pressure which just failed to reach statistical significance (Gerstenberg *et al.*, 1980). A combination of partial denervation and pre-existing bladder outlet obstruction may well produce urinary difficulty after operation. The absence of any significant permanent change in peak flow rate seen in our patients is probably related to a compensatory increase in abdominal straining pressure (Gerstenberg *et al.*, 1980).

The management of these patients should initially be conservative, particularly as abnormal urethral sphincter function has been observed in some of these patients (Sham-Sunder *et al.*, 1978). Some patients, however, may require surgical reduction of their urethral resistance in order to facilitate voiding by abdominal straining (Turner-Warwick and Ashken, 1967; Eickenberg *et al.*, 1976).

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A Controlled Trial of Bladder Drill and Drug Therapy in the Management of Detrusor Instability

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Summary—Fifty women with urinary incontinence due to detrusor instability entered a controlled clinical trial to compare in-patient bladder drill with out-patient drug therapy. Following bladder drill, 84% of patients were continent, whereas following treatment with flavoxate hydrochloride and imipramine, 56% of patients were continent. Side effects due to drug therapy were significant.

The variety of treatments available for idiopathic detrusor instability proves that none is universally accepted as the treatment of choice. Bladder drill, originally advocated by Jeffcoate and Francis (1966), has been shown to be an effective treatment in over 80% of patients (Frewen, 1978; Jarvis and Millar, 1980). Drug therapy is unpredictable, side effects are common and few drugs have been subject to controlled clinical trials (Stanton, 1977). Flavoxate hydrochloride, a commonly used agent, gives a subjective improvement in patients and a reduction in bladder pressure (Stanton, 1973), whilst imipramine has a dual antidepressant and anticholinergic effect (Diokno *et al.*, 1972). There is some evidence that a combination of drugs may be more effective than one alone (Stanton, 1977), although the side effects may also be increased. The aim of this study was to compare in-patient bladder drill with out-patient treatment using a combination of flavoxate hydrochloride and imipramine.

Patients and Methods

Fifty incontinent female patients underwent a full history and examination. Neurological abnormalities, diabetes mellitus and urinary tract infections were excluded, as was any patient taking a drug suspected of affecting lower urinary tract function. Pressure-flow studies were performed by the author; the technique of provocation cystometry was used, filling at 100 ml/min using saline at room temperature. Detrusor instability and all other relevant terminology were defined according to the recommendations of the International Continence Society (1977). No patient had co-existing genuine stress incontinence.

Cystoscopy under general anaesthesia was performed in all cases, partly to exclude local pathology and partly to measure bladder capacity. Each patient was then allocated randomly to one of 2 groups: either in-patient bladder drill, or allowed home and asked to take flavoxate hydrochloride 200 mg tds and imipramine 25 mg tds for 4 weeks. All patients were assessed both subjectively (for frequency, nocturia, urgency and incontinence) and urodynamically after 4 weeks and subjectively after 3 months.

Results

The patients in each group were well matched (Table 1). The symptoms of which the patients complained before and after treatment are shown in Table 2. In the group treated by bladder drill, 21 patients (84%) were continent and 19 (76%) were symptom-free, whereas 14 (56%) were continent and 12 (48%) symptom-free after drug treatment. When these results are compared statistically using χ^2, $x=4.7$ and hence $P<0.05$. When assessed urodynamically, 33 of the 35 patients who had become continent had stable bladders and all patients who remained in-

Table 1 Age and Duration of Symptoms

		Age (years)	*Duration (years)*
Bladder drill group	Range	17-78	1-15
	Mean	47	4.3
	1 SD	15.4	2.7
Drug group	Range	17-65	1-20
	Mean	46	5.4
	1 SD	12.8	3.2

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 2 Symptoms Before and After Treatment

Symptom	*Bladder drill* (n = 25) *Pre*	*Bladder drill* (n = 25) *Post*	*Drug group* (n = 25) *Pre*	*Drug group* (n = 25) *Post*
Frequency	25	6	25	12
Nocturia	21	4	19	13
Urgency	25	4	25	11
Urge incontinence	25	4	25	11
Stress incontinence	19	1	17	9

continent had unstable bladders. The cystometric changes in the volumes causing first sensation and the bladder capacity in successfully treated patients in both groups are shown in Table 3.

Side effects occurred in 14 patients in the drug group (Table 4) and 5 patients (see * Table 4) ceased treatment of their own accord. No patient in the bladder drill group had any side effects.

Discussion

It appears that bladder drill is the most effective treatment available for incontinence due to idiopathic detrusor instability in women (Jeffcoate and Francis, 1966; Frewen, 1978; Jarvis and Millar, 1980).

There is a need, however, for an effective pharmacological treatment for those patients who do not improve with bladder drill, or do not wish to spend time as an in-patient practising drill. The most effective drugs so far have anticholinergic properties with anticholinergic side effects and patients not infrequently choose to cease therapy, preferring incontinence to side effects. It is not clear from this study whether combining 2 drugs, whose modes of action overlap, increases the efficacy or merely the side effects. There is a need for controlled clinical trials to decide on this point.

When symptoms did improve, this improvement was dramatic and occurred within one week of commencing therapy, whether this was bladder drill or drugs. Similarly, all patients who were symptom-free at 4 weeks remained symptom-free at 12. It seems likely, therefore, that if a patient is not significantly improved within 2 weeks of commencing a treatment for detrusor instability, treatment should be changed.

Table 3 Cystometric Values of Patients Before and After Treatment

		Before treatment	*After treatment*
Drill	First sensation (ml)	87	152
(n = 21)	Capacity (ml)	381	470
Drugs	First sensation (ml)	79	140
(n = 14)	Capacity (ml)	353	446

Table 4 Side Effects of Drug Therapy in 14 Patients

Side effect	*Number of patients*
Dizziness	8***
Headache	6*
Dry mouth	6
Nausea	4
Drowsiness	2
Vomiting	1*

Most patients in this study were prepared to tolerate side effects if these occurred but it is difficult to say whether they were due to flavoxate, imipramine or were psychogenic. In no case did side effects persist once therapy ceased.

In this study, urodynamic changes largely mirrored the clinical picture and this has been previously reported both after bladder drill (Frewen, 1978; Jarvis and Millar, 1980) and after therapy with certain drugs including propantheline, flavoxate and imipramine (Diokno *et al.*, 1972; Stanton, 1973).

This is the only known study in which bladder drill is compared with an alternative method of treatment and is further evidence that bladder drill is the treatment of choice for detrusor instability.

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Radiological Trabeculation of the Male Bladder—a Clinical and Urodynamic Assessment

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Summary—Two hundred and fifty patients have been studied by synchronous cine/pressure/flow cystometry to assess the relationship between radiological trabeculation and the urodynamic findings. There is a strong association between detrusor instability and trabeculation. Trabeculation, however, may also occur in the presence of high pressure outflow obstruction, usually at prostate level, in the absence of instability.

It is suggested that frequent uninitiated detrusor contraction against a voluntarily closed sphincter is a likely cause of the more prominent varieties of trabeculation. However, the presence of minor degrees of trabeculation noted at cystoscopic examination in the absence of detrusor instability is not disputed.

Current textbooks of urology and radiology teach that the presence of trabeculation at radiological examination of the bladder is a useful sign in the diagnosis of outflow obstruction in the male (Bailey and Love, 1977; Blandy, 1977; Sutton, 1980). Trabeculation of the bladder has been regarded as work hypertrophy of the smooth muscle of the bladder in response to an increase in outflow resistance.

Recently Gosling and Dixon (1979) have shown that trabeculation of the bladder is not caused by hypertrophy of the smooth muscle bundles of the detrusor but by infiltration of the smooth muscle bundles by connective tissue elements which may be produced by the smooth muscles themselves. They found no evidence to suggest that trabeculation is associated with smooth muscle cell hypertrophy or hyperplasia.

Both Rees *et al.* (1976) and Abrams *et al.* (1976) noted a strong association between radiological trabeculation of the bladder and detrusor instability. Abrams *et al.* (1976) were not able to demonstrate any significant association between outflow obstruction and the presence of trabeculation. In order to investigate further the aetiology of the bladder trabeculation, the urodynamic features of 250 male patients belonging to 4 different diagnostic groups have been studied.

Patients and Methods

The urodynamic results of 4 groups of males who had been investigated by synchronous cine/pressure/flow cystourethrography according to the method described by Bates *et al.* (1970) have been evaluated.

The 4 groups were as follows:

(1) One hundred patients with *trabeculation* of the bladder, irrespective of the urodynamic diagnosis, taken consecutively from the urodynamic clinic.
(2) Fifty patients with urodynamic *normality*.
(3) Fifty patients with detrusor *stable* outflow obstruction due to benign enlargement of the prostate or bladder neck dyskinesia.
(4) Fifty patients with detrusor *unstable* outflow obstruction due to benign enlargement of the prostate or bladder neck dyskinesia.

Detrusor instability was diagnosed according to the criteria laid down by the International Continence Society as a pressure rise during filling cystometry greater than 15 cm/H_2O. A diagnosis of bladder trabeculation was made from the bladder outline on the image intensifier screen, by a consultant radiologist (C.G.W.), at the completion of bladder filling with radio-opaque contrast medium, prior to the voiding study.

Results

Trabeculation of the Bladder and its Urodynamic Implications

One hundred patients with trabeculation were evaluated. Their mean age was 59.7 years (Table 1); 92% were shown to have unstable detrusors on

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Mean Age of Patients Studied

	Number of cases	*Age mean*	*Range*	*Incidence of detrusor instability (%)*
Normal dynamics	50	43.9±14.7	(18-75)	0
Stable outflow obstruction	50	51.9±11.9	(20-74)	0
Unstable outflow obstruction	50	60.5±10.5	(38-76)	100
Bladder trabeculation	100	59.7±14.8	(10-85)	92

Table 2 Radiological Trabeculation of the Bladder

Urodynamic diagnosis	*Stable*	*Unstable*
Outflow obstruction	5	42
Neuropathic	2	21
Enuretic	0	3
Idiopathic	1	26
Total	8	92

n = 100.

filling cystometry (Table 2). Obstruction to the outflow tract was present in 42% of these patients. High voiding pressures were noted in the 42 obstructed patients in this group (Table 3). However, where obstruction was not present the voiding pressures were within the normal range. The aetiology of the instability in the unobstructed cases was attributed to neuropathic causes in 21% and was of idiopathic origin in 26%. Trabeculation and detrusor instability tended to occur in older patients (Table 1).

Table 3 Voiding Pressure in Trabeculated Bladders

	Mean voiding pressure ±ISD (Intrinsic detrusor pressure cm/H_2O)
Unstable unobstructed (n = 30)	44.6±17.8*
Unstable obstructed (n –42)	81.5±36.5*

*P=0.001.

Normal Bladders

Trabeculation was not seen in any of the patients with normal urodynamic studies (Table 4). The patients tended to be younger (Table 1) and their symptom complexes were varied. Prior to the cystometric study, after an initial flow rate on arrival at the urodynamic unit, 14% of these patients were shown to have residual urine on catheterisation (Table 5). However, after the pressure flow voiding study, no patient was seen to have residual urine.

Detrusor Stable Outflow Obstruction

Forty per cent of this group of patients had trabeculated bladders. Trabeculation was associated with the symptoms of frequency, nocturia and urgency of micturition in the absence of detrusor instability (Table 6). It is possible that instability may be present in some patients with trabeculation who are shown to have stable bladders on filling cystometry. Some patients may fail to demonstrate abnormalities of detrusor function during filling cystometry even when provocative tests are applied. Patients with trabeculation had significantly higher detrusor voiding pressures than those patients with normal bladder outlines (Tables 4 and 7). The position of the outflow obstruction was more likely to be at prostatic level than at bladder neck level when trabeculation was present (Table 8).

Detrusor Unstable Outflow Obstruction

The age incidence in this group of patients was

Table 4 Trabeculation and Voiding Pressures Related to Outflow Obstruction

	Incidence of trabeculation (%)	*No trabeculation voiding pressure cm/H_2O±ISD*	*Trabeculation voiding pressure cm/H_2O±ISD*
Normal bladders (n = 50)	0	48.8±9.3	—
Stable outflow obstruction (n = 50)	40	74.1±25.7*	93.8±38.3*
Unstable outflow obstruction (n = 50)	74	74.1±27.3	72.8±24.4

*P=0.05.

Table 5 Significance of Residual Urine Values

	Normal dynamics	*Stable outflow obstruction*	*Unstable outflow obstruction*
Number of cases	50	50	50
Cases with initial residual urine after initial flow rate (%)	14	48	38
Residual urine (mean vol ml)	117 ± 57	342 ± 429	196 ± 236
Cases with residual urine after pressure flow voiding study (%)	0	50	32
Post-voiding study. Residual urine (ml ± ISD)	0	184 ± 219	90 ± 87

Table 6 Stable Outflow Obstruction and Trabeculation Symptom Complex

	Trabeculated cases (%)	*No trabeculation cases (%)*
Frequency	63	19
Nocturia	63	13
Urgency	32	3
Poor stream	53	55

60.5 years (higher than that of other groups) (Table 1). Seventy-four per cent were seen to demonstrate trabeculation. The mean voiding pressures in the presence or absence of trabeculation were the same (Table 4). Frequency, nocturia and urgency of micturition were common symptoms with an incidence of 57% in the presence of trabeculation and 77% in its absence. The site of the obstruction to the outflow in both stable and unstable bladders was more likely to be in the prostatic urethra (Table 8). However, in non-trabeculated stable obstructed bladders, bladder neck obstruction was more common.

Discussion

Abrams *et al.* (1976), noted a significant association between detrusor instability and trabeculation but could not demonstrate any relationship between outflow obstruction and trabeculation. The results of this study confirm a very strong association between detrusor instability and radiological trabeculation. However, in the absence of instability high pressure outflow obstruction may also produce the same effects on the detrusor smooth muscle and therefore the radiological appearance of trabeculation. The presence of recurrent uninitiated detrusor contractions against a voluntarily closed sphincter is possibly the cause of the changes in the appearance of the bladder muscle, but hypertrophy of the muscle is not the feature. Why the changes in the smooth muscle of the detrusor occur is not clear. The degree of trabeculation noted on radiological examination is obviously severe; however, lesser degrees of trabeculation seen at cystoscopic examination represent earlier changes in the spectrum of trabeculation and these may be the result of outflow tract obstruction. The patients with high pressure stable outflow obstruction in this series who showed signs of trabeculation tended to be older (mean age 60.6 years) than those patients without trabeculation.

The relationships between increasing age, outflow obstruction and detrusor instability are confirmed by analysis of the results of this study (Table 1).

Trabeculation tends to occur in older patients and is strongly related to the presence of detrusor instability and to raised detrusor pressure outflow obstruction. In younger patients one can expect to see obstruction more commonly at bladder neck level and the symptoms of frequency, nocturia and urgency in the absence of infection are much less common.

The value of excretion urography in patients with symptoms of prostatic obstruction has been questioned. If trabeculation is present, detrusor

Table 7 Stable Outflow Obstruction and Trabeculation

(Mean values) ± ISD	*Stable trabeculated*	*Stable normal bladder*
Initial residual (ml)	118	81
Voiding pressure (cm/H_2O)	93.8	74.1
Flow rate (ml/s)	8.6	9.3
Post CMG residual (ml)	95.3	98.5

Table 8 Outflow Obstruction and Trabeculation: Site of Obstruction

	Trabeculation cases (%)		*No trabeculation cases (%)*	
	Stable	*Unstable*	*Stable*	*Unstable*
Bladder neck	32	40	77	30
Prostate	68	60	19	70

instability should be suspected. A clinical history with special regard to the symptoms of frequency, nocturia and urgency of micturition may make one more suspicious of the presence of detrusor instability. If a diagnosis of outflow obstruction is also made, patients can be warned that their symptoms of frequency, nocturia and urgency may persist after surgery to relieve their outflow obstruction, if their instability does not revert. (This may occur in up to 20% of cases.)

Residual urine seen on the post-micturition films of intravenous urograms in the presence of trabeculation should suggest the associated presence of outflow obstruction. Residual urine does not usually occur in normal individuals (Table 5). The pre-cystometry residuals seen in the group of "normal" patients studied could be due to incomplete efforts to void in unfamiliar surroundings or to the presence of unfamiliar noises and people. We find that encouragement to void after filling cystometry in the majority of patients with normal urodynamic studies will lead to complete bladder emptying. The presence of more than 50 ml residual urine should suggest incomplete emptying of the bladder. The intravenous urodynamogram described by Turner-Warwick *et al.* (1979) enabled a useful simple "urodynamic" assessment to be made. Provided the patient is allowed time to accumulate sufficient urine in the bladder to enable a satisfactory flow rate, and is permitted to void in a quiet environment, a final view of the bladder will demonstrate the presence or absence of residual urine. The presence of the grosser features of trabeculation at radiological examination will act as a predictive feature of abnormalities of detrusor function. In the absence of urodynamic studies, a careful symptom history, an intravenous urogram and a flow rate will demonstrate the presence of lower urinary tract obstruction and indicate whether detrusor instability is likely, if trabeculation is present.

Trabeculation of the male bladder seen at radiological examination is a useful predictive feature of the presence of detrusor instability and the high pressure forms of outflow tract obstruction.

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The Early Changes in the Development of Bladder Cancer in Patients Exposed to Known Industrial Carcinogens

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Summary—In the Huddersfield district many people have been exposed to industrial carcinogens as a result of their occupation. An exfoliative urine cytology screening programme has been in operation for many years so that patients with the early changes associated with these carcinogens are referred for urological investigation at a very early stage in the disease.

A description of the development of urothelial dysplasia, carcinoma *in situ* and transitional cell carcinoma is presented with particular reference to the urine cytology, histological features of mucosal biopsies and cystoscopic appearances of the bladder. Changes in the collagen fibres in the basement membrane are also described.

The survival rate of early stage bladder cancer in the Huddersfield Health District is poorer than that in the neighbouring district of Bradford, although the Huddersfield patients were of a slightly younger age group and presented earlier (Cartwright *et al.*, 1980). Further epidemiological surveys have shown that workers subjected to known industrial carcinogens have up to a 10 times greater chance of developing bladder malignancy (Glashan and Cartwright, 1981); the particular carcinogens in this area are naphthylamine, magenta, auramine and benzidine. Our interest in this particular aspect of bladder cancer has been stimulated over the years because of the difficulties that these patients present both in diagnosis and in treatment; in this district there have been at least 5 chemical works associated with these carcinogens, and over the years nearly 200 cases of bladder cancer have occurred in workers who were thought to have been exposed to carcinogens.

In order to diagnose the early stages of bladder cancer, routine exfoliative urine cytology has been performed in several works' populations for many years, the cytology being performed at least twice a year and, in some cases, with equivocal results, on a more frequent basis. This has enabled us to study in more detail some 25 patients who presented at the very early stages of malignant disease of the urothelial system and, as a result, we believe that there are 3 stages in the disease process which may take many years to develop fully. This study, which will take years to complete, suggests that the initial changes are those of atypical urine cytology associated with histological evidence of urothelial dysplasia; this is followed by a deteriorating cytological picture associated with carcinoma *in situ* and, finally, the development of an obvious malignancy of the bladder which, in this particular group of patients, is almost always associated with a high degree of invasion.

Patients and Methods

The routine screening of potentially exposed workers has given us a unique opportunity of studying the disease at a very early stage, since these patients are referred to the urological clinic with atypical cells in their urine without any urological symptoms. The usual symptoms of bladder malignancy, *e.g.* frequency, haematuria and dysuria, are never seen at this early stage.

The industrial screening process is entirely dependent on exfoliative urine cytology and for this we use the usual Papanicolaou grading I-V as follows:

Class I (normal)—Normal transitional cells in sparse numbers.
Class II (atypical)—Transitional cells present in in-

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creased numbers but normal morphology or smaller transitional cells or an increased number of leucocytes and histiocytes with or without bacteria indicating either infection or inflammation.

Class III (suspicious)—Abnormal epithelial cells present with enlarged and/or hyperchromatic nuclei, not fulfilling malignant criteria.

Class IV (probably malignant)—Abnormal epithelial cells with features resembling malignant cells (abnormal nuclei/cytoplasmic ratio, hyperchromatic nuclei).

Class V (malignant)—Cells present in the urine with all of the criteria of malignancy.

In the presence of active urinary infection or with large numbers of leucocytes in the urine, great care must be exercised in diagnosing malignancy. It is also our experience that any specimen of urine in the presence of a well established invasive bladder malignancy will reveal malignant cells but, in the simpler tumours of the Ta or T1 category (UICC, 1978), few cells with malignant characteristics may be found in the urine. Carcinoma *in situ* is also associated with large numbers of malignant cells, but to diagnose the initial changes of urothelial dysplasia, concentrated early morning specimens of urine should be used, for if the cytology is equivocal (*e.g.* Grade III) this may well be missed if a diluted specimen is taken during the day; furthermore, early staining of the first voided urine is to be recommended, since the early changes in the cytological picture may not be observed if a postal system of urine cytology is employed without using a preservative (Glashan and Riley, 1980). The assessment of urine cytology is directly related to the experience and ability of the observer and accuracy can be obtained only with experience.

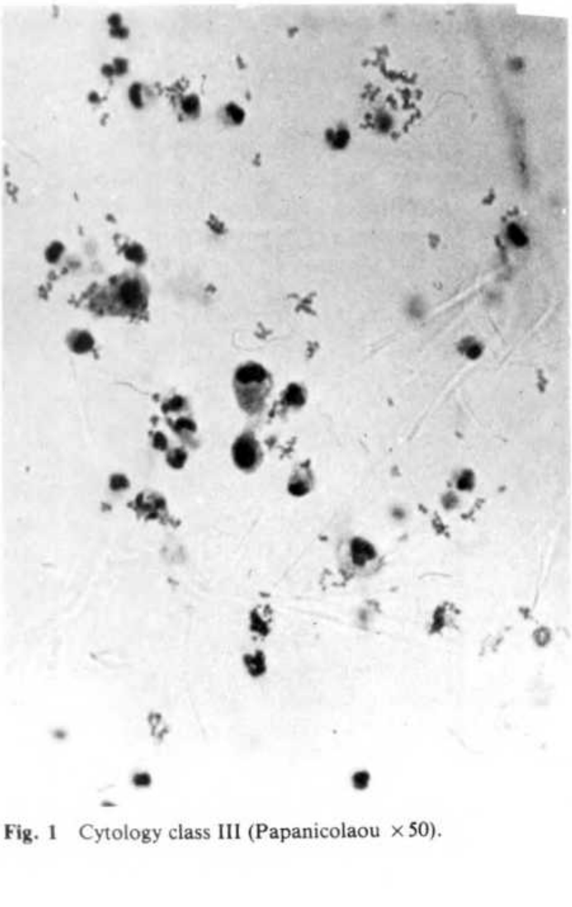

Fig. 1 Cytology class III (Papanicolaou ×50).

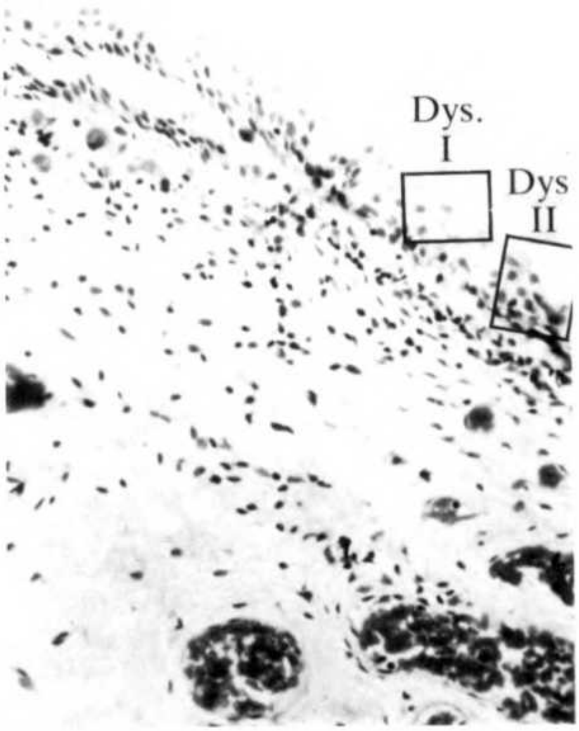

Fig. 2 Early dysplasia (H and E ×8).

The Initial Stage—Urothelial Dysplasia

If one assumes that all patients have normal urine cytologies with a normal bladder and normal transitional cell epithelium, the first change noted is that the urine cytology exhibits an increased number of cells of a fairly normal cell type which on further observation tend to become slightly abnormal with enlarged and/or hyperchromatic nuclei (Fig. 1). These cells suggest that changes are occurring in the bladder mucosa and it is at this stage that the patients are referred to the urological clinic. Although asymptomatic, they are investigated routinely with intravenous urography, full blood count, electrolytes, urine culture and further cytological assessment. The patients are then advised to have a cystoscopy under a general anaesthetic which invariably shows a normal looking bladder mucosa. Routine multiple mucosal biopsies, however, show a varying degree of urothelial change which we classify as dysplasia. Hyperplasia may be present, but this really means a hypertrophy of normal urothelial cells and is usually part of a healing process when the bladder has been subjected to some form of trauma (Hicks and Chowaniec, 1978); dysplasia is a much more disorderly pattern of growth in the cellular structure of the mucosa (Fig. 2). Other non-malignant conditions in the urinary tract can simulate this condition, *e.g.* a stone in the renal pelvis or bladder or chronic infection of the urinary tract, but removal of the stone or resolution of any underlying infection will lead to the return of a normal cytological pattern, whereas it is our experience that urothelial dysplasia associated with exogenous carcinogens is a progressive condition. The only other abnormality that may be noticed is that on microscopy the urine may show an increased number of red blood cells.

We have divided dysplasia into 3 groups on an empirical basis, indicating the degree of histological change which could be observed under the microscope which we describe as mild, moderate and severe (Grades I-III). The initial mucosal change shows an increased irregularity of the surface cells with a break in the continuity almost certainly due to a decrease in the number of desmosomes, which are intercellular junctions providing sites of strong adhesions between epithelial cells. We believe that this decrease in cell adhesion contributes to the increased sloughing of the surface cells and thus the increase in the cellular deposits observed in dysplasia and in carcinoma *in situ*. These conditions involve wide areas of the bladder epithelium but in the more localised Ta and T1 tumours this increase in the cellular deposit is much less evident and this agrees with the findings of Alroy *et al.* (1981), who found that the desmosomal densities were increased in the non-invasive superficial transitional cell carcinomas but decreased in the more invasive carcinomas where there is a larger area of tumour.

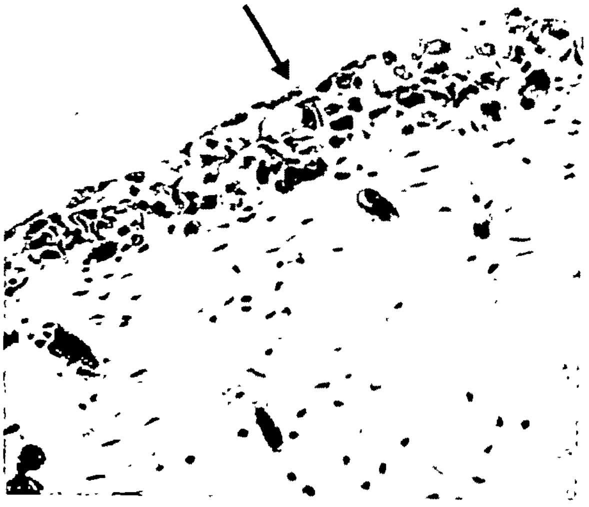

Fig. 3 Advanced dysplasia (H and E ×8).

In these early dysplastic changes, the staining reaction of the basal cells becomes more prominent and there is less order in the deeper cell areas. There is a marked increase in the number of blood vessels in the submucosa. As these changes progress into the Grade II dysplasia there is a more marked staining reaction of the cells and an increase in the irregularity of the surface cells. There is also an increase in the cellular reaction at mucosal level and these changes progress until, in the more severe degrees of dysplasia (Grade III), all cell layers show a very marked staining reaction with or without an increase in mitotic figures and a disorderly pattern of the cells occurs with a loss of polarity (Fig. 3).

All changes of dysplasia may be seen in the same biopsy specimen, including that of the next stage in the process, namely carcinoma *in situ* as previously reported (Glashan, 1974). All cases of dysplasia are not necessarily due to underlying malignant change but, in our experience, the more severe degrees of dysplasia undoubtedly progress to develop a malignant urothelium and it is only in the early Grade I dysplasias that reversal can occur, where the cause is calculus disease or chronic infection. Radiotherapy and the use of intravesical agents have also been incriminated in the development of dysplasias but in our experience a Grade III advanced degree of dysplasia is always associated with a progressive change towards malignancy and we suggest that it should be called malignant urothelial dysplasia.

Second Stage—The Development of Carcinoma In Situ

Patients with dysplastic change in the bladder and

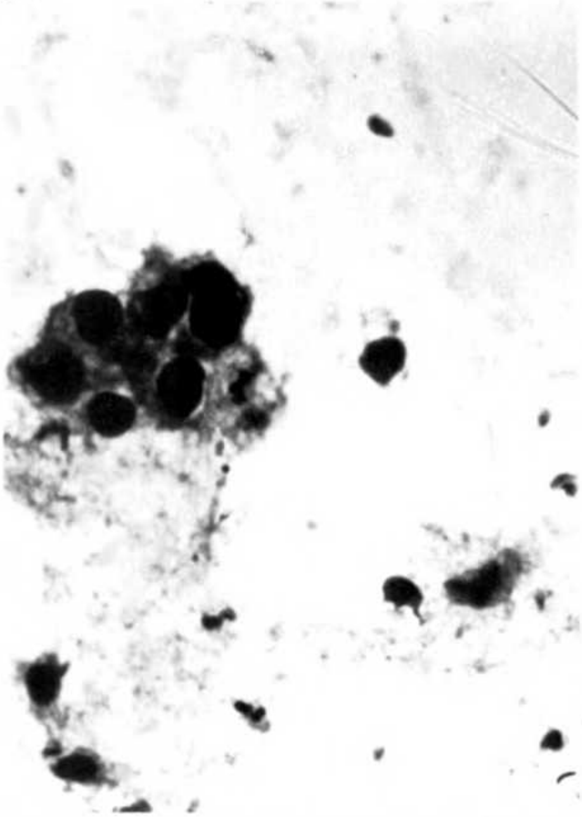

Fig. 4 Cytology class IV. Carcinoma *in situ* (Papanicolaou ×50).

abnormal cytology are kept under observation, often for many years, and in time the next stage of the disease is the development of carcinoma *in situ*, where the nuclear size shows a marked variation with associated hyperchromatism, irregularities of the nuclei and coarse aggregates of chromatin; the cytoplasmic/nuclear ratio becomes abnormal, *i.e.* the nucleus becomes progressively larger in relation to the cell which is in itself much bigger than the normal cell type, and these in terms of Papanicolaou grading become classified as Class IV (Fig. 4).

At cystoscopy, the bladder may show several areas of mucosal reddening which may simulate patchy areas of inflammation which initially are quite flat but in time these tend to become raised. In our experience, when the mucosa becomes raised, this is the first time that patients will tend to complain of urinary symptoms, with increased frequency of micturition and occasional dysuria, particularly at the end of micturition. As the carcinoma *in situ* becomes more widespread the mucosal changes become more obvious and widespread; this is usually associated with more severe frequency. Biopsy of these lesions, which tend to

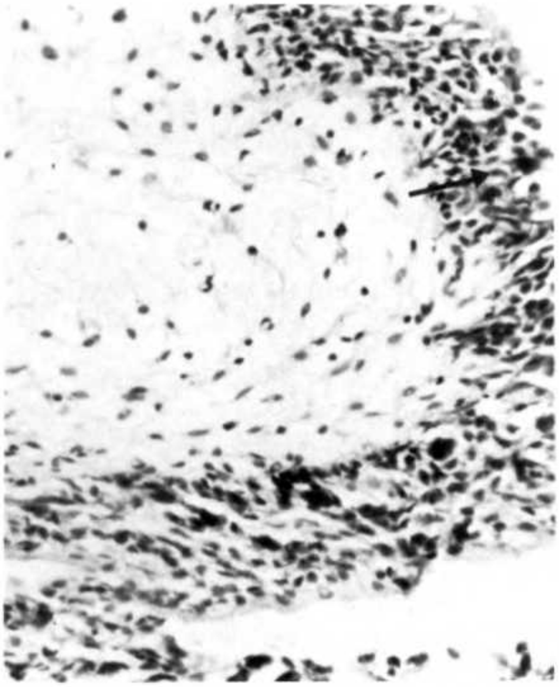

Fig. 5 Carcinoma *in situ* (H and E ×20).

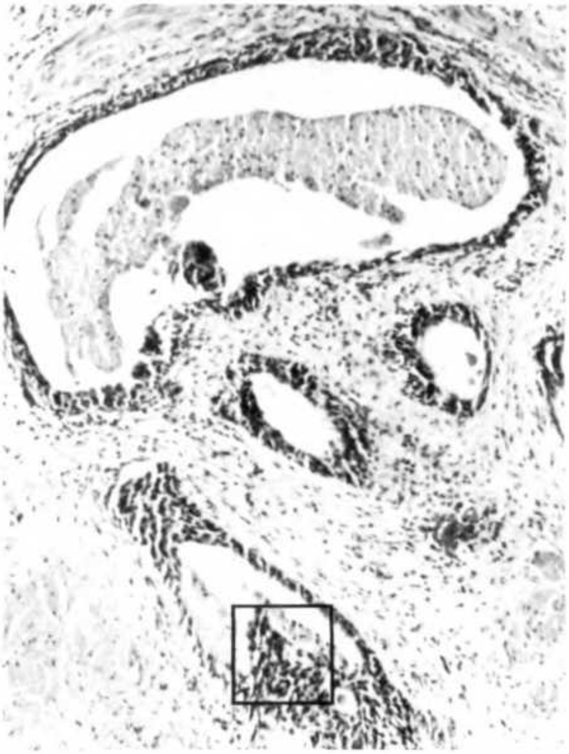

Fig. 6 Carcinoma *in situ* in mucosa and Brunn's nest (H and E ×8).

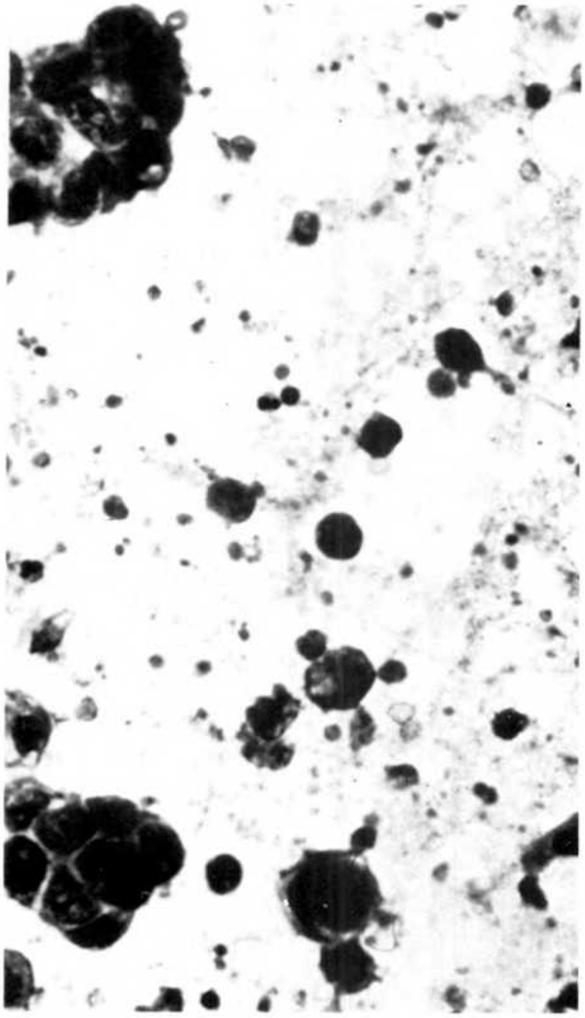

Fig. 7 Cytology class V. Carcinoma (Papanicolaou × 50).

be found on the posterior wall or around the ureteric orifices or just posterior to the bladder neck, demonstrate the typical histological pattern of carcinoma *in situ* (Fig. 5). Histologically, the changes of carcinoma *in situ* are often associated with a marked shedding of the epithelial cells into the bladder, so that the mucosa may be only one or 2 cells in thickness; there may or may not be a marked increase in the basal cell layers but there is no invasion of the basement membrane. Should histological sections pass through a Brunn's nest, marked changes of carcinoma *in situ* may be noted but in these nests the epithelial shedding, previously mentioned in the mucosa, are often not obvious and the nests may be lined with many layers of deeply staining cells (Fig. 6). Cytologically, the picture is that of a Class V in the Papanicolaou grade (Fig. 7).

Final Stage—The Development of Carcinoma

The final stage in the development of tumour is the appearance at cystoscopy of a bladder carcinoma which tends, in patients who have been exposed to industrial carcinogens, to be widespread, highly aggressive and invasive from the onset. Although these tumours occasionally appear to be relatively benign, invasive changes are usually found at the base of the tumours and in most cases the tumour is a transitional cell carcinoma, but a few do tend to develop squamous cell change, presumably due to a de-differentiation of the cell type. Cytologically the urine shows large numbers of highly malignant Grade V cells on the Papanicolaou grade.

Time Scale in the Development of Bladder Cancer

It has been known for many years that there is a long latent period between exposure to industrial carcinogens and the actual development of a bladder tumour. This time scale, which is very variable, may well be dose-related, although this is a difficult aspect of the problem to look at retrospectively. We have examples of an invasive bladder tumour developing within 10 years of exposure and, at the other extreme, 40 years have elapsed between exposure and malignant change. The stage of urothelial dysplasia is much more difficult to assess for it is impossible to know when it starts and when it finally merges with carcinoma *in situ*, since both conditions may coexist. Once carcinoma *in situ* is established the time scale shortens and it is usually a year to 18 months before a tumour will develop. Here again, however, the time scale is variable, and we have histological evidence of a case of carcinoma *in situ* lasting for as long as 10 years before tumour formation finally occurred; another patient progressed from carcinoma *in situ* to invasive carcinoma within 4 months. When the carcinoma finally supervenes, it is usually a matter of months before invasion takes place.

Basement Membrane

The basement membrane is a thin, uninterrupted layer separating the epithelium of the bladder from the lamina propria below. Although it lies close to the base of the basal layer it cannot be seen readily in the routine H and E stains, but only in

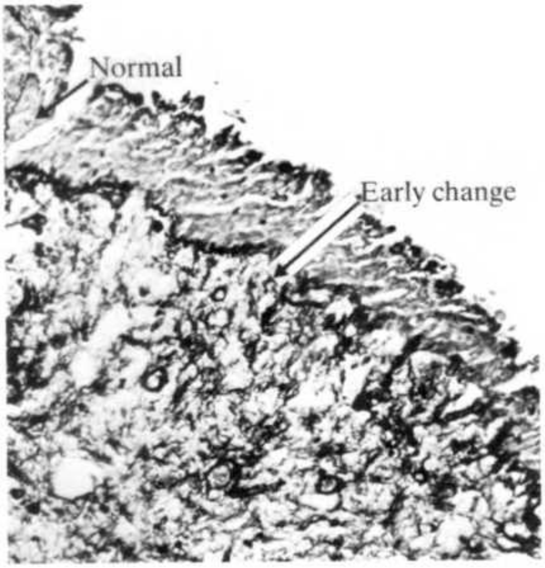

Fig. 8 Early disruption of collagen fibres in basement membrane (Methenamine ×20).

well prepared special stains of Methenamine Silver. This latter stain is selectively picked up by collagen fibres that make up this layer.

In some cases of industrial exposure, even with minimal epithelial damage, *e.g.* Grade I or Grade II dysplasia, marked changes can be seen in this basal layer and in some the basal lamina may be completely absent. This lamina consists of mainly collagen fibres and these appear to lengthen and to develop a wavy appearance which progresses to disruption of the fibres, which eventually fragment and disappear (Figs. 8 and 9). These changes appear to be much more pronounced in people who have been exposed to exogenous carcinogens and its disappearance may be related to early invasion by the malignant process. We believe that the basement membrane may act as a restricting process to the transgression of carcinoma and that when the collagen fibres are disrupted (collagenolysis), the ability of the bladder to restrict the invasiveness of the tumour becomes impaired. We intend to investigate collagenolysis on a prospective basis on patients presently under study who have been subjected to industrial carcinogens.

We consider that carcinogens eventually lead to the development of urothelial dysplasia, the more severe degrees of which should be regarded as

Table Proposed Classification of Industrial Bladder Neoplasms

Stage	*Cytology*	*Cystoscopy*	*Histology*
0	Normal I PAP.	Normal	Normal transitional cell epithelium
1	Suspicious III PAP.	Normal	Dysplasia
2.	Malignant characteristics IV/V PAP.	Reddened mucosa (may be raised)	Carcinoma *in situ*
3	Malignant V PAP.	Tumour seen	Carcinoma

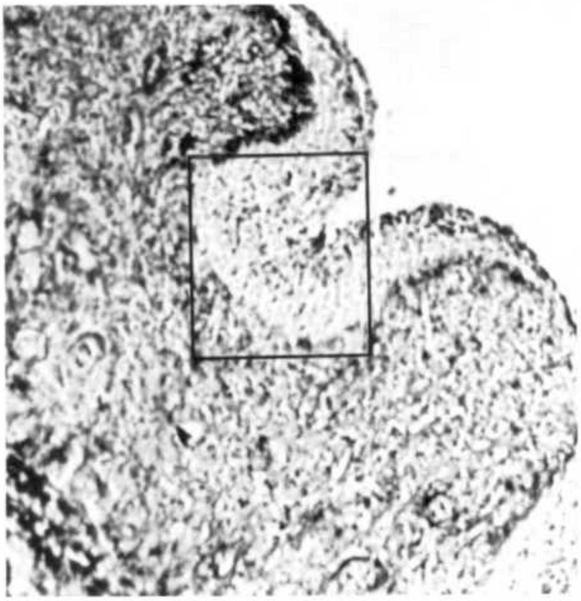

Fig. 9 Progressive basement membrane changes; almost complete disruption in carcinoma *in situ* (Methenamine ×20).

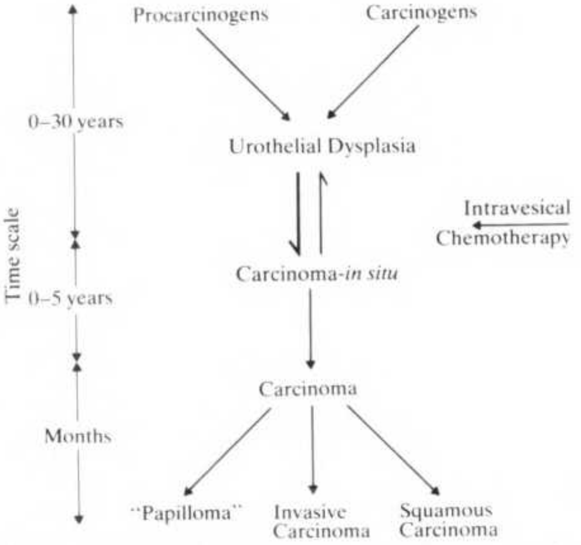

Fig. 10 The development of bladder neoplasia following exposure to carcinogens.

pre-malignant. These dysplastic changes progress to carcinoma *in situ* and finally carcinoma of the bladder which tends to become invasive at an early date. These changes can be monitored by exfoliative urine cytology in conjunction with serial mucosal biopsies of the bladder even though the patient may be asymptomatic with a normal-looking bladder at cystoscopy. These changes are summarised in the Table. In the cases we have studied so far, constant reproducible findings were the changes in the basement membrane and the disruption of the collagen fibres. These changes tend to be progressive with eventual disappearance of the basement membrane. A suggested classification of the build-up of carcinoma in patients subjected to exogenous carcinogens is suggested (Fig. 10).

The significance of these changes in the progression of this pre-malignant state to an invasive carcinoma needs to be studied over many years on a prospective basis, but the early diagnosis of these pre-malignant states has become more important recently with the use of intravesical doxorubicin (Adriamycin). A group of these patients has now been treated for over a year and the preliminary results suggest that some of these changes can be reversed (Glashan and Riley, 1981).

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The Clinical Significance of Tissue Polypeptide Antigen (TPA) in the Urine of Bladder Cancer Patients

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Summary—A 2-stage study has been carried out to evaluate the usefulness of urinary tissue polypeptide antigen (TPA) levels in patients with bladder cancer as an adjunct to the routine procedures for detection of bladder tumours. Two-hour urine samples were collected from 83 bladder cancer patients and normal individuals for the first part of the study, 24-h samples from 54 patients and normal individuals for the second part. Urinary TPA was determined using radioimmunoassay. In 2-h samples there was no significant difference in the amounts of TPA/l in any of the groups.

In contrast, the TPA results of 24-h urine samples (n = 54) were markedly different from 2-h samples and the former correlated very well with the presence or absence of bladder cancer. A reason for this difference may be circadian rhythm effects.

Tumour markers such as carcinoembryonic antigen (CEA) may be of equivocal value in predicting the presence or recurrence of malignant disease (Turner *et al.*, 1977; Schuster *et al.*, 1978). However, studies related to a lesser known substance, tissue polypeptide antigen (TPA), have given encouraging results (Björklund *et al.*, 1973; Menendez-Botet *et al.*, 1978; Nemoto *et al.*, 1979; Björklund, 1980; Lüthgens and Schlegel, 1980). Recently we found that sera from apparently healthy male workers exposed to bladder carcinogens (*i.e.* a population with a significant risk of developing bladder cancer) and hospitalised patients with bladder cancer contained significantly raised levels of TPA compared with age-matched healthy volunteers (Kumar *et al.*, 1978).

The present study was initiated to investigate whether estimations of urinary TPA levels in patients with bladder cancer have a practical value as an adjunct to the routine procedures used in the detection of urinary bladder tumours.

TPA is heterogeneous in nature and SDS-polyacrylamide gel electrophoresis resolves it into components with molecular weights ranging from 45,000 to less than 20,000 (Lüning *et al.*, 1980). Thus TPA is capable of being filtered through the kidneys and excreted in the urine (Isacsson and Andren-Sandberg, 1977; Menendez-Botet *et al.*, 1978).

The amino acid sequences of the biologically active part of TPA are known and synthetic polypeptides based on such sequences exhibit specific activity *in vitro* (Redelius *et al.*, 1980). The antigenic determinants contain tyrosine and arginine. Most of the previous studies on estimation of TPA have been carried out using the haemagglutination inhibition technique. Recently, Björklund *et al.* (1980) developed a radioimmunoassay to measure TPA and found very good agreement between the results obtained by haemagglutination inhibition and radioimmunoassay. In the TPA radioimmunoassay none of the following cross-reacted with TPA: carcinoembryo antigen, α-fetoprotein and Tennagen.

Patients and Methods

All urine specimens were collected in Huddersfield and Manchester for this 2-stage study (Table 1). In the initial part, urines were 2-h samples from 83 individuals. In the second stage of the investigation 24-h urines were collected from 54 patients and normal donors. All persons with systemic or urinary tract infections and those showing any signs of renal failure were excluded from the study. Soon after collection the samples were coded and stored frozen at −20°C. Frozen coded samples

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Details of Urine Samples Studied

Source of urine	*Number of 2-h urine samples (1st stage study)*	*Number of 24-h urine samples (2nd stage study)*
1. Patients with bladder cancer		
(*a*) tumour present	21	19
(*b*) tumour absent	34	15
2. Controls: patients with urogenital disease (excluding infections) and healthy volunteers	28	20
Total	83	54

were packed in solid carbon dioxide (—80°C) and shipped to Stockholm for TPA analysis. The TPA analysis was done blind, *i.e.* the Stockholm laboratory did not know the identification code given to the samples. Prior to the estimation of TPA, urinary pH was adjusted to 7.3±0.2 by the addition of 0.2M NaOH or HCl. One part of urine (150-200 μl) was mixed with an equal part of dilute phosphate buffered saline containing 1% bovine serum albumin, pH 7.3.

Urinary TPA was determined using a radioimmunoassay kit (AB Sangtec Medical, Box 20045, S-161 20 Bromma, Sweden). The basic principle of the assay is the sequential saturation of anti-TPA antibody, first by TPA in the specimen and then by ^{125}I-TPA. The bound radioligand is separated by precipitation with rabbit anti-horse antibody. The radioactivity in the precipitate is measured in a gamma counter. The percentage bound radioligand is calculated from a standard curve (Fig.). In all of the samples tested the standard deviations were found to be less than 10%. Values higher than or equal to 85 units/l were considered positive. The rationale for this cut-off level has been discussed previously (Björklund *et al.*, 1980). The TPA assay is standardised with reference to healthy Swedish blood donors to give at least 95% of the values below an empirically established TPA cut-off level of 85 units/l. This means that the probability of a healthy blood donor exhibiting a TPA value below 85 units/l is 95%. These values have consistently held true for several years.

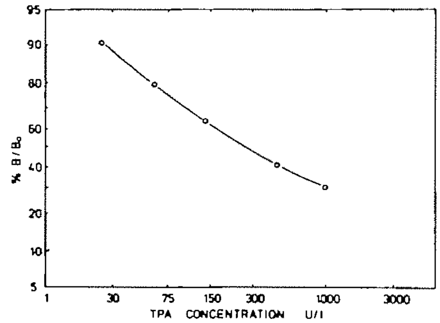

Fig. Standard curve for radioimmunoassay of TPA obtained using commercially available kits (Santec Medical).

At the time of the collection of urine samples, each patient was examined by endoscopic and radiological techniques to establish the diagnosis and the extent of the disease. Cytological examination of urine was also carried out in patients with haematuria where no transitional growths were found by other methods.

Results

The analysis of results on 2-h urine samples from 83 individuals who formed the first part of the study showed that although the amount of TPA/l was higher in tumour-bearing bladder cancer patients (698±270), there was no significant difference between the 3 groups. In addition, the groups did not differ from each other when a cut-off level of 85 units/l was used to determine the proportions of positive samples (Table 2, column 1). The distribution of TPA values was not normal; therefore data were also logged but on statistical analysis, once again the 3 groups could not be distinguished from each other.

The analysis of data from 24-h urine samples showed that these results were markedly different from the 2-h samples and the former correlated well with the clinical diagnosis. The details of controls and patients together with their TPA values are shown in Tables 1 and 3. From these tables it is apparent that in 18 out of 19 cases

Table 2 TPA Analysis of 2-h Urine Samples (Stage 1 Study)

Source of urine	*No. positive/ no. tested*	*Actual TPA units/100 ml urine (mean ± SD)*
1. Patients with bladder cancer		
(*a*) tumour present	13/21 (62%)	698 ± 1636
(*b*) tumour absent	18/34 (53%)	230 ± 330
2. Controls: patients with urogenital disease (excluding infections) and healthy volunteers	15/28 (54%)	189 ± 270

Table 3 TPA Analysis of 24-h Urine Samples (Stage 2 Study)

Source of urine	*No. positive/ no. tested*	*Actual TPA units/1000 ml urine (mean ± SD)*
1. Patients with bladder cancer		
(*a*) tumour present	18/19* (95%)	524±392
(*b*) tumour absent	0/15† (0%)	34±24
2. Controls: patients with urogenital disease (excluding infections) and healthy volunteers	1/20 (5%)	32±27

UICC (1978) pathological classification.

* Seven cases with pTaG1, 11 cases with pT1G2 and one case with pT2G3 tumours.

† Eleven cases with pTaG1, one case with pT1G2 and 3 cases with pT2G3 tumours.

where the tumour was present, their urinary TPA values were above the cut-off level (mean 524±392), the exception being one patient with tumour pT1G2 (UICC (1978) classification) whose urinary TPA level was lower (81 units) than the cut-off level of 85 units. None of the 15 patients who were clinically free of bladder cancer had more than 85 units/l (mean 34±24). Similarly, with the exception of one individual (95 units/l), the remaining 19 controls had TPA levels lower than 85 units/l.

Discussion

Previous serum-TPA estimations on more than 3000 normal people and cancer patients have shown that a significantly higher proportion of patients with known metastatic cancer (73±10%) had raised levels of TPA compared with healthy donors (2±1%) (Bjorklund *et al.*, 1973; Björklund, 1980). Furthermore, a highly significant correlation was found between survival and TPA serum values. Temporary elevation of serum TPA levels has been observed among 20% of hospitalised patients with inflammatory and infectious diseases. However, these temporary elevations return to normal once the patients have completely recovered. Bjorklund *et al.* (1978) and Björklund (1980) pointed out that any results with a raised level must be confirmed to exclude the possibility that it was not a temporary disease. Persistently raised levels or a return to raised levels to above the cut-off level in known cancer patients would warrant a thorough re-examination of an individual for the presence or recurrence of tumour. It is relevant to mention 3 individuals (classified as controls, but not included in the tables) who initially attended the urology clinic and on examination were found to have no detectable bladder cancer. Their TPA values were found to be 1000, 103 and 1000 units/l. On follow-up the first patient was found to be suffering from chronic renal failure, the second patient had squamous cell carcinoma of the skin and the third patient had carcinoma of the pancreas. These patients could not be regarded as controls and were therefore excluded from the study.

The most significant finding of the present study is that in patients with urothelial cancer, urine can be used for the estimation of TPA, but to be of practical value it is necessary to test 24-h urine samples since a distinction cannot be made between cancer-bearing and cancer-free patients using the 2-h samples. The reason for this difference might be diurnal variation (circadian rhythm). Diurnal variation in the urinary CEA level has also been reported (Kodama *et al.*, 1979). We would emphasise that however promising the present results appear, they are based on a small number of patients and controls. A much larger series needs to be investigated for satisfactory evaluation before recommending routine TPA testing of the urine in the management of carcinoma of the bladder. Such studies are in progress.

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Prophylactic Oral Methotrexate Therapy for Multiple Superficial Bladder Carcinoma

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Summary—Sixteen patients with multiple, frequently recurring Ta/T1 transitional cell carcinoma of the bladder were treated with methotrexate syrup 50 mg orally every week for 18 months. In 11 patients the frequency, number and size of tumour recurrences decreased markedly. In 3 patients the incidence of tumour recurrence appeared unchanged and in 2 patients the disease progressed and required cystectomy. Overall, the average number of tumours recurring per patient month at risk fell significantly from 2.6 to 1.2 while taking methotrexate.

It is suggested that oral methotrexate may provide an effective alternative to intravesical chemotherapy for the prevention of recurrent superficial bladder carcinoma.

The primary treatment of multiple superficial tumours in the bladder is endoscopic resection. With modern resectoscopes there are few superficial bladder tumours that cannot be resected completely, so that the role of intravesical chemotherapy as initial treatment of such tumours is now limited.

Most urologists recognise that the probable importance of intravesical chemotherapy is its use as prophylaxis to prevent tumour recurrence. Conventional intravesical chemotherapy requires repeated urethral catheterisation for the instillation of cytotoxic agents and is associated with the irritative symptoms of chemical cystitis in a significant proportion of patients. In an attempt to avoid these disadvantages a cytotoxic drug was sought which could be taken orally and would be sufficiently excreted in the urine to provide effective chemo-prophylaxis. Methotrexate was considered a suitable agent as it is absorbed satisfactorily from the stomach at low dosage and, although partly metabolised by the liver and bound to plasma proteins, is excreted mainly unchanged in the urine. Based upon the pharmacodynamics of this agent and normal urine excretion patterns, it was calculated that 50 mg methotrexate administered orally could yield cytotoxic levels in both the plasma and urine for several hours, exposing the tumour to the drug for a longer period than could be achieved by intravesical instillation.

Patients and Methods

Patients with multiple, frequently recurring T1 transitional cell carcinoma who had had multiple tumours at each cystoscopy for one year or more were treated with methotrexate syrup 50 mg orally each week for 18 months. Follow-up cystoscopy was performed at approximately 3-monthly intervals to assess the incidence and frequency of tumour recurrence and compared with the tumour recurrence pattern for one year prior to commencing methotrexate therapy.

All patients were assessed initially by cystoscopy, bimanual examination and biopsy, together with confirmation of normal renal function, liver function and peripheral blood count. All visible tumour was resected completely. Full blood count was performed each week before administration of methotrexate and the dose was withheld if the total white cell count fell below 3000 or the platelet count below 100,000. At the time of each cystoscopy renal and liver function were reassessed and a chest X-ray was performed.

Results

Sixteen patients have been treated and each has completed at least 18 months' therapy with methotrexate (Table 1). In 11 patients the frequency and number of recurrent tumours has been reduced considerably. In 3 patients tumours continued to develop at a rate similar to that prior to methotrexate, although they continue to be managed endoscopically. In 2 patients the treatment

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Clinical Evaluation of Success of Oral Methotrexate Therapy in 16 Patients with Ta/T1 Bladder Carcinoma

Results: Prophylactic therapy
11 Tumour incidence reduced
3 Tumour incidence unchanged
2 Tumour progressed→T3 after 3/12 →mT1 after 11/12
Total 16

failed as their disease progressed and more radical treatment was required: one patient developed an invasive T3 tumour within 3 months and the other continued to develop multiple superficial recurrences for which cystectomy was performed at 11 months.

Table 2 shows the pattern of tumour recurrence in greater detail. Comparing the pattern of tumour recurrence before and during treatment by the Wilcoxson Signed Rank test, the incidence and frequency of tumour recurrence has been reduced significantly during methotrexate treatment. Considering the group of 16 patients as a whole, the number of tumour-free cystoscopies has increased from 2/61 to 21/65, although no patient has been rendered permanently tumour-free. Conversely, the number of tumours found at each cystoscopy has decreased from 10.1 to 4.4. Probably the most relevant method of analysis is the number of tumours developing per patient month at risk and this has been reduced from 2.6 to 1.2 tumours per month.

Toxicity

Only one incident of serious toxicity occurred and that was in a patient who misunderstood the instructions and took 50 mg methotrexate daily for one week. He developed severe oral and skin ulceration, moderate diarrhoea, leukopenia and thrombocytopenia, but all symptoms and signs subsided with appropriate Leucovorin therapy. The patient has subsequently received methotrexate 50 mg weekly without further toxicity.

Table 2 Pattern of Tumour Recurrence in Patients Receiving Prophylactic Oral Methotrexate Therapy

	Before MTX	*Prophylactic MTX*
Number of tumour-free cystoscopies	2/61	21/65
Number of tumours per cystoscopy	10.1	4.4
Number of tumours per patient month at risk	2.6	1.2

All other patients have remained relatively undisturbed by their methotrexate. Two complained of mild oral ulceration following their first or second dose but this has not occurred with subsequent doses. Three had nausea which they attributed to the methotrexate syrup; 3 complained of burning discomfort in the eyes which was relieved by Leucovorin eye drops but has not interfered with therapy. Over 1200 doses of weekly oral methotrexate have been administered and only on 3 occasions has therapy been deferred because of thrombocytopenia. Significant leukopenia has not been observed.

Discussion

In this type of study it is difficult to ensure that the patients treated are comparable with those of other trials. In this study recruitment was limited to patients with frequent recurrences who were becoming difficult to manage endoscopically and who, under normal practice, would be treated by cystectomy. The results of a number of trials of prophylactic chemotherapy in this situation, including thiotepa, Adriamycin, VM-26 and pyridoxine, have been reported. Different authors have assessed their patients in different ways but whichever factors are considered, the patients in our study were a particularly "bad" group (Table 3). Ninety-seven per cent of cystoscopies of our patients prior to methotrexate revealed recurrent tumours compared with only 17 to 31% in other trials. The recurrence rate per 100 patient months at risk was 25 compared with 5.7 to 10.5 and the time to develop a single recurrence was only 0.38 months compared with 2.66 months (Burnand *et al.*, 1976; Gavrell *et al.*, 1978; Byar, 1979; Schulman, 1979).

The concentration of methotrexate in the urine of patients in this study varied considerably but in all cases urinary methotrexate concentration reached cytotoxic levels for at least 8 h and in many patients for 24 h (Fig.), verifying that an oral dose of 50 mg methotrexate yields cytotoxic concentrations for a longer period than can be achieved by intravesical instillation.

The regime is free from serious toxicity and could be used in a larger patient population without undue risk.

This study has not been a definitive trial as there were no randomised controls. It was a Phase

Table 3 Comparison of Untreated Patients in Present Study and Previous Published Reports of Prophylactic Intravesical Chemotherapy

Author	*Cystoscopies showing recurrence (%)*	*Recurrence rate per 100 patient months*	*Time to develop one recurrence (months)*
Byar (1979)	17	5.7	—
Schulman (1979)	30	10.0	—
Gavrell *et al.* (1978)	31	10.5	—
Burnand *et al.* (1976)	—	—	2.66
Hall—present study	97	25.0	0.38

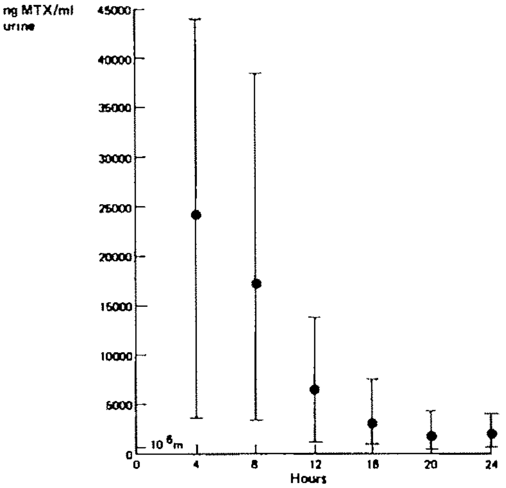

Fig. Concentration of methotrexate in the urine of patients receiving 50 mg methotrexate syrup orally (mean + range).

II type of study, seeking limited evidence of anti-tumour activity, and although treatment failed in 5/16 patients it was very encouraging in 11/16.

Methotrexate appears to offer a potentially effective form of prophylactic therapy for superficial transitional cell carcinoma and should be tested in a prospective cross-over trial against placebo.

Acknowledgements

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A Controlled Trial of Single Dose Intravesical Adriamycin in Superficial Bladder Tumours

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Summary—Sixty patients with recurrent superficial bladder tumours (Ta or T1) entered an open controlled trial of single dose Adriamycin. After transurethral resection of tumour recurrences, patients were alternately allocated to the control group or to the Adriamycin group, who received an instillation of 50 mg of Adriamycin in 50 ml of saline for 30 min. Six months later all patients were readmitted for endoscopy.

In the Adriamycin group significantly more patients showed a decrease in the number of recurrent papillomas (72%) than in the control group (39%). This study shows that the use of adjuvant chemotherapy in the form of single dose Adriamycin is effective in reducing tumour recurrence.

Superficial bladder tumours may be considered in 3 clinical groups:

1. The single tumour which tends not to recur.
2. Multiple tumours which recur frequently but remain under endoscopic control.
3. Multiple tumours which invariably recur and are difficult or impossible to control endoscopically.

This study has been confined to the second group of patients. Approximately 100 patients with frequent multiple tumour recurrences are under regular review in our unit. Such patients are admitted at 6-monthly intervals for endoscopy and resection of their recurrences. Frequent admission and surgery are disruptive for the patient and consume a considerable part of hospital bed-time and operating time. Each anaesthetic has its known small risk and repeated resection into the bladder wall may lead ultimately to extensive fibrous replacement of bladder muscle with consequent symptoms of frequency and nocturia.

We have looked to adjuvant chemotherapy to ease the burden placed on both patient and hospital resources by these tumours. The aim of the study was to evaluate the effect of single dose Adriamycin doxorubicin and to see whether it allowed a decrease in the frequency of endoscopy.

Methods

Sixty patients, aged 53 to 84 years, entered an open trial of Adriamycin versus no treatment. Patients were placed alternately in each group. For inclusion in the trial the following was required: histologically confirmed superficial bladder tumour (pTa or pT1) and the presence of bladder tumours at both of the patient's previous 2 endoscopies, that is 12 months and 6 months before their entry into the trial. The stage and differentiation of the tumours is given in Table 1. In addition, the patients were required to have normal routine haematology and biochemistry screening tests. There was no significant difference in the ages, sex distribution, time from first diagnosis of tumour, or in the proportion of previous positive endoscopies between the Adriamycin and control groups (Table 2). The mean number of previous endoscopies was 8.7 in the Adriamycin group and 7.5 in the control group.

Table 1 The Pathological Stage and Histological Grade of 60 Patients in the Adriamycin and Control Group

Stage	*Ta*		*T1*	
Differentiation	*Well*	*Moderate*	*Well*	*Moderate*
Control (30 patients)	17	6	2	5
Adriamycin (30 patients)	15	7	6	2

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 2 The Mean Age, Sex Distribution, Mean Time from Initial Diagnosis and Mean Percentage of Previous Positive Endoscopies in 60 Patients in the Adriamycin and Control Groups

	Mean age	*Sex distribution (%)*		*Mean time from diagnosis*	*Mean % previous positive endoscopies*
		M	*F*		
Control (30 patients)	68	79	21	5.8 years	92
Adriamycin (30 patients)	72	70	30	6.6 years	91

All patients were endoscoped and their tumours noted for position, size and number. If the patient had more than 15 tumours, it was difficult to count them accurately. Such patients, for the purposes of analysis, were said to have 15 tumours.

All tumours were fully resected. A 22 FG, 3-way irrigating catheter was left in the bladder overnight. Next day, before the catheter would have been removed, 50 mg of Adriamycin dissolved in 50 ml of normal saline were instilled into the bladder. The catheter was left clamped for 30 min before the bladder was drained and the catheter removed. The occurrence of bladder pain during instillation was noted. A blood count was repeated by the patient's general practitioner 7 days later.

Six months later the patient was readmitted for review endoscopy. At this visit the number and size of any tumours was recorded and the tumours resected in the normal way.

Results

Twenty-eight patients in the control group completed the study, one patient being lost to follow-up and readmission of the other being delayed. Twenty-nine patients in the Adriamycin group were followed up: the exclusion of the single patient was because of immediate severe bladder pain on instillation of Adriamycin, necessitating immediate drainage of the bladder.

The results are expressed in 3 different ways. Firstly, by whether or not the tumours had "responded" or not (Table 3). There was a significant improvement in the Adriamycin group ($\chi^2 = 6.1$, 1 df, $0.02>P>0.01$). Secondly, the response was described according to the categories shown in Table 4. The data given refer to analysis done on the number of tumours. The sub-groups are too small for statistical analysis. Thirdly, the mean number of tumours at the onset and termination of the trial are given in Table 5.

Table 3 Number of Patients Showing Decreased Number of Tumours (responded) or the Same or Increased Numbers (no response) in 57 Patients who Completed the Study

	Responded	*No response*
Control (28 patients)	11	17
Adriamycin (29 patients)	21	8

There was a low incidence of side effects. Only one patient had severe bladder pain on Adriamycin instillation, although 6 patients had bladder discomfort for up to 24 h after instillation. The haematological studies were incomplete but in no case was a change in the full blood count noted.

The response to Adriamycin did not appear to be related to any recognised pre-treatment factors, such as number of bladder tumours, stage of tumour (pTa or pT1), or to the histological differentiation of the tumours.

Discussion

Large numbers of compounds have been assessed in the treatment of superficial bladder tumours. Adriamycin was selected for this study because previous studies suggested it was effective and relatively free from side effects (Banks *et al.*, 1977; Edsmyr *et al.*, 1980). The present study was constructed with the specific object of reducing the number of hospital admissions for bladder tumour. For this reason the present EORTC trial of Adriamycin versus Epodyl versus placebo would have placed an unmanageable workload

Table 4 The Degree of Response, Measured by Number of Tumours, in 57 Patients who Completed the Study

	No recurrence	*>50%*	*<50%*	*No change*	*Worse*
		Improved			
Control (28 patients)	3	4	4	8	9
Adriamycin (29 patients)	6	10	5	7	1

Table 5 The Mean Number of Tumours per Patient at the Outset of the Study, Compared with the End of the Trial Period. Data From the 57 Patients who Completed the Study

	Number of tumours	
	At start of study	*At end of study*
Control (28 patients)	7.2	7.1
Adriamycin (29 patients)	8.3	5.2

on our department (EORTC, 1979). This trial is costly in terms of materials and hospital bedtime, since the protocol requires catheterisation and drug instillation 15 times with 4 endoscopies in the first year. There remains an obligation to continue close follow-up of each patient indefinitely. The EORTC trial allows inclusion of all superficial bladder tumours, be they single or multiple tumours, or patients presenting for the first time or with recurrent tumours. In our view, such intensive treatment may be better reserved for those patients with multiple recurrences who are out of endoscopic control, or who show signs of going out of control, as suggested by Riddle (1973) in the case of Epodyl treatment. We have not considered such patients to be within the scope of this study. There appears to be no trial of Adriamycin comparable with the present study, although a similar study was carried out using thiotepa. The thiotepa study showed that fewer patients in the treated group developed recurrent tumour.

In the present study we have attempted to define precisely the pathological stage of the tumours treated. We have not included carcinoma *in situ* patients (Tis) as these patients may often have a much worse prognosis due to the development of invasive bladder cancer. Random bladder mucosal biopsies have not been performed in this study and therefore Tis changes cannot be excluded. During the course of the study the difficulties of assessing the actual size of tumours became apparent, so that the number of tumours was used as the only measure of response. Certain aspects of our methodology may be questioned. The instillation time of 30 min was used because it was felt that a longer period of instillation the day after resection might lead to an unacceptable absorption of Adriamycin. However, the absorption studies done by other workers have shown that significant absorption is unlikely (Eksborg, 1979). We think, therefore, that an instillation time of 60 min would be safe. Adriamycin did not come into contact with the urethral mucosa, the patients being asked not to void the bladder contents at the end of the instillation period. No patient in this study had urethral tumours; furthermore, by draining the bladder after the instillation period we could be sure that the bladder would not be exposed to Adriamycin longer than we had intended, if the patient could not void at the end of the instillation period.

Adriamycin may be active by preventing implantation of tumour cells released during resection of tumours or by altering a bladder mucosa which is capable of developing superficial bladder tumours. It does appear able to influence the behaviour of a bladder mucosa predisposed to forming bladder tumours, as shown by the beneficial effect of Adriamycin on carcinoma *in situ* (Edsmyr *et al.*, 1980; Jakse and Hofstadter, 1980).

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Early Multiple-dose Adjuvant Thiotepa in the Control of Multiple and Rapid T1 Tumour Neogenesis

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Summary—In 45 patients each with a well established and constant pattern of widespread tumour neogenesis following cystodiathermy, early multiple dose adjuvant thiotepa was used in an effort to control the tumours.

The response was good in 32 patients as judged by the reduction in the number of new tumours and by the downgrading and downstaging of new lesions when compared with pre-thiotepa histology. Continuing maintenance therapy was required in the majority but, with the passage of time, the dosage could be progressively reduced, suggesting a cumulative effect of treatment.

Of 13 non-responders, 7 showed evidence of higher than average malignant potential against which thiotepa appears ineffective.

The timing of administration is probably a key factor in success and one which accounts for much of the variation in reported results.

Among T1 bladder cancer patients those who exhibit a continuing high rate of tumour neogenesis are the most difficult to control. Eventually some undergo cystectomy simply because of the quantitative aspect of the problem and it is in this group that intravesical chemotherapy would seem to promise most. Reports on the effectiveness of intravesical thiotepa vary considerably but overall they are encouraging when the agent is used as an adjuvant to cystodiathermy (Burnand *et al.*, 1976).

In a group of patients proving difficult to manage by cystodiathermy alone, we have used quickly repeated instillations of thiotepa given soon after clearance of all visible tumour in an attempt to prevent further tumours and this paper reports our experience.

Patients and Methods

Forty-five patients were treated, 31 men and 14 women, with an average age of 62 years. In each the clinical problem was one of many new tumours at every check cystoscopy despite previous complete endoscopic clearance (Fig. 1).

Tumours were classified according to the TNM system (Table 1).

The length of documented tumour history before starting thiotepa was less than 2 years in 12 patients, 2 to 5 years in 24 and more than 5 years in 9.

Thiotepa Regime

All tumours were meticulously resected and following the regime suggested by Oravisto (1972), 30 mg of thiotepa in 50 ml of saline was instilled for 2 h on post-operative days 1, 3 and 5. The dose was to be reduced to 15 mg if pre-treatment blood counts indicated toxicity but in practice this was not necessary.

Cystoscopy was repeated 3-monthly, when any new tumours were resected and thiotepa repeated. It was planned to give one further course after a patient responded, a measure not always carried out, and then to reduce or stop thiotepa according to individual minimum requirement.

Table 1 Adjuvant Thiotepa. Patients Treated. Tumour Grade and Stage

Grade	*Stage*		*Totals*
	pTa	*pT1*	
G1	17	12	29
G2	4	12	16
Totals	21	24	45

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

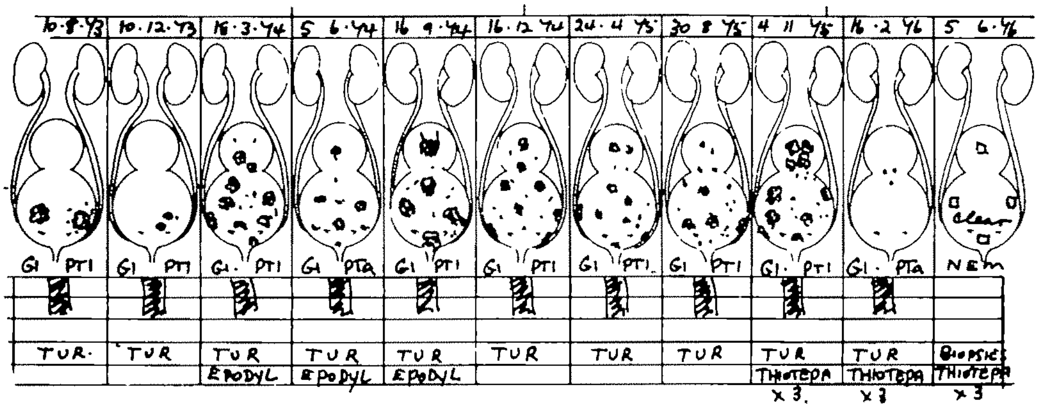

Fig. 1 Characteristic clinical problem of many new tumours at every cystoscopy Marked reduction in numbers after first course of thiotepa and clear after second

Follow-up ranged from 1 to 5 years, with 29 patients followed for 3 or more years and an overall mean of 3 years: 3 patients moved away after 1, 2 and 3 years respectively

Assessment of Results

It was a clinical necessity to use thiotepa as a routine in all of these patients, so that there are no controls. Experience has shown, however, that the degree of new tumour activity in these patients is highly unlikely to alter when treatment is by cystodiathermy alone, so that the well established pre-thiotepa pattern of tumour growth formed a sound basis on which the results of thiotepa therapy were assessed.

Results

Responders

If after a maximum of 3 courses of treatment the bladder became tumour-free or if new tumour numbers were reduced to a small fraction of established pattern, a patient was considered to have responded. Most patients had somewhere near 20 or more tumours at each cystoscopy before treatment, so that 3 tumours or fewer were considered a satisfactory response (Fig. 1).

On this basis, 32 patients responded. Response was better when lamina propria was not involved (PTa) but there was no difference between grades G1 and G2 (Table 2).

Eight patients remained tumour-free when thiotepa was stopped. The number of courses of treatment received and the patients involved were 1×3, 2×2 and 3×3. One patient died from other causes after only 6 months and the longest tumour-free period now stands at 4 years. All but one patient belonged to G1 category and most were in stage pTa (Table 3).

The remaining 24 responders needed routine maintenance therapy. With the passage of time, however, the common pattern of response allowed for progressive reduction in thiotepa dosage. Fewer instillations were needed in a course of treatment and cystoscopies could be spaced increasingly further apart, suggesting a cumulative effect of therapy (Fig. 2). Two of this group died from urothelial tumour, one from lung metastases (G1 pTa) 2 years after responding to thiotepa and 20 years after presentation, and the other from a G3 renal pelvis tumour, 4 years

Table 2 Adjuvant Thiotepa Response by Grade and Stage

Grade	*Stage*					
	pTa		*pT1*		*Totals*	
	Responders	*Non-responders*	*Responders*	*Non-responders*	*Responders*	*Non-responders*
G1	13	4	8	4	21 (72%)	8
G2	4		7	5	11 (69%)	5
Totals	17 (81%)	4	15 (63%)	9	32 (71%)	13

Table 3 Adjuvant Thiotepa. Responders Tumour-free Without Maintenance

Grade and stage	*Periods tumour-free*
G1 pTa × 5	6 months (d.o.c.) 1*, 2, 3*, 4 years
pT1 × 2	2, 3 years
G2 pT1 × 1	2 years
8	

*Moved away

Table 4 Adjuvant Thiotepa. Responders Requiring Maintenance Therapy

Frequency	*Numbers of instillations and patients*		
3-monthly	×3	4	
	×2	2	8
	×1	2	
6-monthly	×3	3	
	×2	5	15
	×1	7	
annually	×1	1	1
			24

Includes 2 tumour deaths (M1 lungs, renal pelvis tumour). Periods on maintenance 1 to 5 years, average 3 years.

after a response in the bladder. Seventeen have been followed up for 3 or more years, the longest now at 5 years (Table 4).

When a patient responded, a common pattern was a dramatic fall in the number of new tumours after the first course of thiotepa, often followed by complete clearance after a second (Fig. 1). If thiotepa was stopped and subsequently needed to be restarted, except in 2 cases, patients always responded again just as well (Fig. 3). The 2 cases of failure to respond a second time are shown only as non-responders.

Downgrading and Downstaging

Among the 16 patients presenting with G2 tumour, 9 showed an improvement in grade to G1 in new tumours grown after thiotepa. Five had a stage improvement as well, from pT1 to pTa. Two of the 9 continued to grow tumours in numbers which classified them as non-responders (Table 5) (Fig. 3).

Non-Responders

Thirteen patients did not respond. The initial histology conformed to the pattern of the series and gave no hint of outcome which was fatal in 5 (Table 6).

Deaths

There were 7 deaths from urothelial tumours, including one in a renal pelvis, giving a tumour death rate of 16%. Three others died from unrelated causes.

Table 5 Adjuvant Thiotepa: Improvement in Grade and Stage

Before Thiotepa	*After Thiotepa*
G2 pTa × 4	G1 pTa × 2
G2 pT1 × 12	G1 pTa × 5 pT1 × 2
16	9 (56%)

Includes 2 non-responders who showed grade improvement.

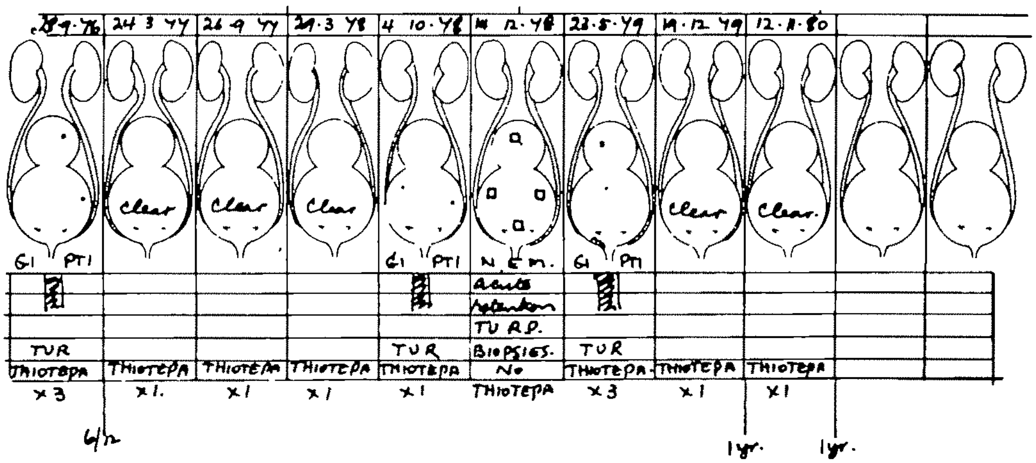

Fig. 2 Continued tumour flow-card of Figure 1: cumulative effect of thiotepa with continuing improvement on diminishing dosage.

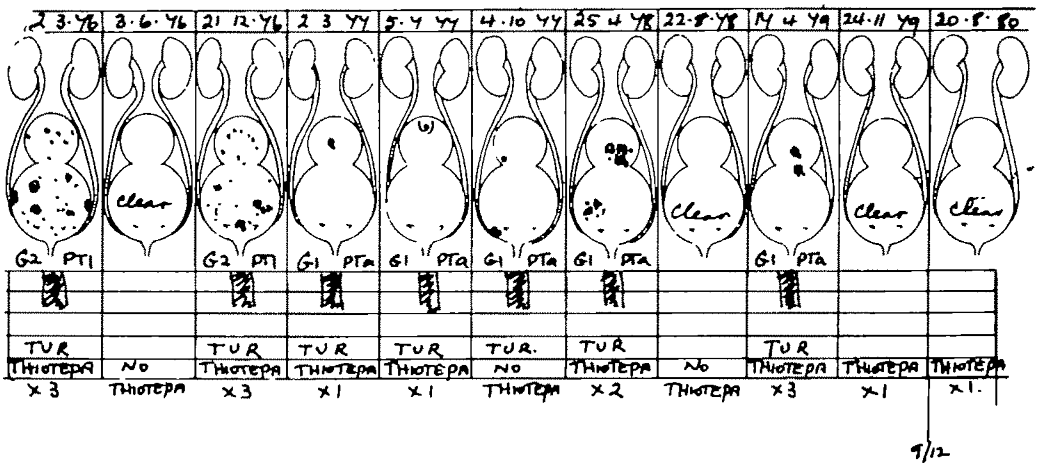

Fig. 3 Renewed response when thiotepa restarted and effect of dose on tumour formation. Tumour downgrading and downstaging as a result of therapy.

Toxicity

Despite instillation within 24 h of extensive resections, there was no evidence of toxicity due to absorption of thiotepa. There were a few complaints of bladder discomfort but no treatment had to be stopped.

Discussion

Several different treatment regimes have been used for adjuvant thiotepa and reported results vary widely (Westcott, 1966; Pavone-Macaluso, 1971; Oravisto, 1972; Burnand *et al.*, 1976). Most authors have used a single dose repeated at regular intervals but waiting up to one month after resection before starting thiotepa. However, if it is accepted that new tumours arise mainly from areas of urothelial dysplasia (Melamed *et al.*, 1964; Soloway *et al.*, 1978; Murphy *et al.*, 1979) and some probably from tumour cell implantation (Soloway and Masters, 1979), then it seems more appropriate to give thiotepa soon after endoscopy, when the lesions are at their smallest and presumably their most vulnerable. When thiotepa was given early in tumour development in animal model experiments, new tumours were often of a lower grade and stage (Murphy and Soloway, 1980) and that was true for our patients too (Table 5). Tumour cells are vulnerable to thiotepa when they are undergoing mitosis and instillations, quickly repeated, may be a means of placing more cells at risk.

The most obvious effect of early, multiple-dose thiotepa was the dramatic drop in new tumour numbers seen at cystoscopy in 70% of patients. It has commonly been assumed that this effect results mainly from the destruction of areas of abnormal urothelium which otherwise would have progressed to overt tumours. Recently, however, Murphy and Soloway (1980) reported that in animal model experiments thiotepa did not prevent the development of tumours from dysplastic epithelium. In an earlier experiment, an effect of

Table 6 Adjuvant Thiotepa. Non-responders, Subsequent Clinical Course

Outcome		*Histology when treatment started*
Died from bladder cancer, increase in Grade to G3, muscle invasion, distant metastases	4	G1 pTa×1 pT1×2 G2 pT1×1
Developed urothelial upper tract tumours	3	G1 pTa×2 (1 died) pT1×1
Status unchanged or improved	6	G1 pTa×1 pT1×1 G2 pT1×4 (downgraded to G1×2)
	13	

thiotepa was shown to be an increase in degeneration and exfoliation of abnormal cells and applying these findings to man, the authors suggested that the apparent reduction of new tumour numbers after thiotepa may be because many of the new tumours are made invisible at cystoscopy due to increased exfoliation, while the neoplastic process itself is not significantly altered.

It is difficult, however, to correlate this hypothesis with the clinical course of those patients who apparently responded to thiotepa. In 8 patients no further tumours were seen after thiotepa had been stopped and follow-up in 6 ranged from 2 to 4 years. It is hard to believe that in these previously very active bladders intact neoplastic processes made invisible because of increased exfoliation would continue to remain invisible for up to 4 years after the agent responsible had been discontinued. In those who required maintenance therapy the picture is one of steady, progressive improvement achieved on a diminishing thiotepa requirement, a picture strongly suggestive of a change in urothelial behaviour. Also, in other patients we have used thiotepa successfully to control flat, *in situ* carcinoma of G2 grade. Before therapy, urine cytology was always positive, whereas afterwards no malignant cells could be found, a finding difficult to reconcile with the persistence of an active neoplastic process of this grade.

Thirteen patients continued to grow many new tumours despite thiotepa, their behaviour apparently being like that seen in the animal model. The range of histology conformed to the rest of the series but already 7 have progressed to G3 grade or muscle invasion or have developed urothelial tumours of the upper tracts and, as a result, 5 have died. The factor which sets them apart from the responders appears to be a higher degree of malignant potential. Similarly in the animal model experiments, an appreciable number died from tumour early in the experiments, an indication that the induced dysplasia and subsequent tumours were of a uniform high malignant potential also. In man, the overall potential and tumour death rate is low and the animal model results appear to be applicable only to that limited proportion of T1 patients who have higher than average malignant potentials and who apparently do not respond to thiotepa either.

In our experience early multiple dose adjuvant thiotepa has controlled active, widespread T1 tumour neogenesis in a high percentage of cases. In those who respond, the clinical course appears to support the premise that thiotepa prevents areas of dysplasia from progressing to overt tumours and it probably acts as prophylaxis against implantation of tumour cells as well. In addition it seems to have a "reprogramming" effect on the urothelium, resulting in a progressive reduction of malignant potential. This is manifested by a slowing down of neoplastic activity and, in a significant number of patients, by the downgrading of any new tumours formed, a result of which should prevent some cases of progression in the future. Clinical evidence suggests that non-responders have a higher than average malignant potential against which thiotepa is not effective.

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The Correlation of T1 Bladder Tumour History with Prognosis and Follow-up Requirements

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Summary—The histories of 332 T1 bladder cancer patients were studied to determine the natural history in this tumour population. Each was followed for at least 5 years or to earlier tumour death and the approach to treatment was conservative.

Patients were potentially at serious risk of disease progression and death if they presented with tumours of G2 or G3 grade and grew new ones again after treatment or if they exhibited a continuous high level of tumour neogenesis. Fourteen developed urothelial tumours beyond the bladder, evidence of widespread urothelial instability. Tumour deaths accounted for only 12% of the series, justifying a conservative approach to treatment, and a further 25% died from unrelated causes.

Those remaining tumour-free at 5 years had a low malignant potential and their natural history supported discontinuing routine cystoscopy after that time.

The supervision of T1 bladder cancer is the most time-consuming single item in urological practice. The disease encompasses a wide spectrum of malignant potential, ranging from no more than inconvenience at one end to a fatal outcome at the other. A prerequisite to rational management is a clear understanding of the natural course of the disease.

This study is an attempt to determine the medium to long term natural history of a T1 tumour population and to identify factors which are important in prognosis and to the conduct of follow-up.

Patients and Methods

Among patients presenting with the disease between 1960 and 1975 were 332 who attended regularly and who had each been followed for at least 5 years or to earlier tumour death and they form the basis of this study.

Ages ranged from 23 to 85 and 69% were in the 2 decades 50 to 69 years. Men outnumbered women by 3 to 1.

Patients were assessed according to the requirements of the TNM system and details of grade and stage are shown in Table 1. Single tumours were present in 239 (72%) and they were multiple in 93 (28%).

Treatment

Approach to treatment was conservative. Broad guidelines followed consisted of endoscopic resection for G1/G2 tumours with the addition, since 1972, of adjuvant intravesical thiotepa in very active bladders. G3 tumours received radical radiotherapy, as did G2 tumours not otherwise controlled. The main indication for cystectomy was residual tumour after radiotherapy and only 16 cystectomies were performed for T1 tumour.

Length of follow-up ranged from 1 to 20 years. Twenty-one patients died from tumour within 1 to 4 years and the remaining 311 were followed for 5 or more years, with 119 being supervised for 10 years or longer. The average follow-up time in these 311 patients was 9 years.

Table 1 Grade and Stage at Presentation

Grade	*Stage*		*Total*	*(%)*
	pTa	*pT1*		
G1	135	105	240	72
G2	5	59	64	19
G3		28	28	9
Total	140	192	332	

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 2 Response to Initial Treatment: Incidence and Multiplicity of New Tumours by Grade and Stage

Response to treatment	*G1*		*G2*		*G3*	*Totals*	*(%)*
	pTa	*pT1*	*pTa*	*pT1*	*pT1*		
Growing new tumours							
Single	38	15	1	18	7	79	24
Multiple	56	60	2	29	6	153	46
Total	94	75	3	47	13	232	70
Remaining tumour-free	41	30	2	12	15	100	30
Totals	135	105	5	59	28	332	

Table 3 Appearance Times of First New Tumours by Degree of Activity

Time interval	*Degree of new tumour activity*			*Total (%)*
	Single tumours (%)	*Multiple tumours*		
		Low activity (%)	*High activity (%)*	
Within				
3 months	9	17	69	30
1 year	41	54	97	63
2 years	63	74	100 (within 15 months)	78
5 years	85	89		91
After 5 years (mean 8 years)	15	11		100
Mean	2.5 years	2.0 years	<6 months	232

Results

Outcome after Initial Treatment

Seventy per cent grew tumours again after initial clearance. Two-thirds of these had multiple tumours present on at least one occasion and the remainder grew new single tumours one or more times. Neither grade nor stage had any effect on the liability to grow new tumours. The relatively good performance of G3 category reflects the benefit of radiotherapy (Table 2).

New Tumour Activity

Judged by numbers and speed of appearance, new tumour activity varied enormously. On this basis the 153 patients who grew multiple new tumours on at least one occasion could readily be divided into 2 groups. One group of 82 showed relatively low activity, always having fewer than 5 small tumours at any cystoscopy and often none at all. Only 17% had new tumours at 3 months and the average time of first appearance was 2 years (Fig. 1). In contrast, the other 71 always had more than 5 tumours at every 3-monthly cystoscopy and commonly the bladder was studded with growth. By 3 months 69% had new lesions and no patient was tumour-free beyond 15 months (Fig. 2). Once a pattern of activity was established it usually did not change.

In the series as a whole, appearance times ranged from 3 months to 14 years and with increasing new tumour activity these times became shorter (Table 3).

Patients growing a first new tumour after 5 years numbered 21 and all but one (G2.pT1) were of G1 category and all reproduced identical tumours.

Disease Progression

Any change in disease status which places the

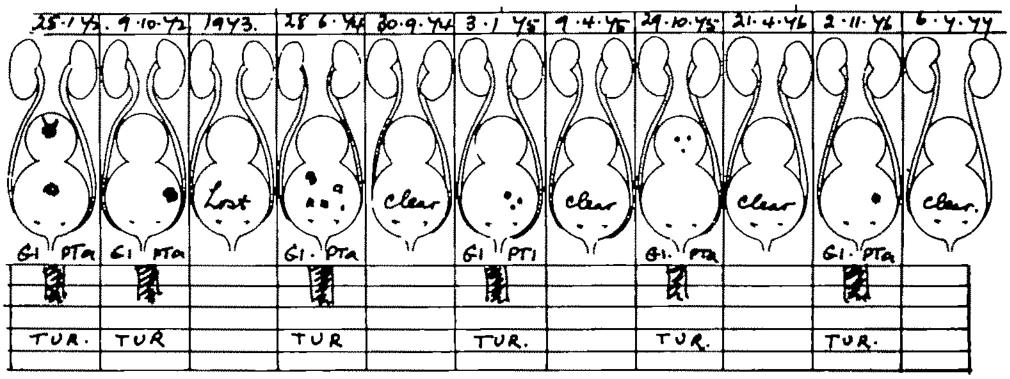

Fig. 1 Multiple new T1 bladder tumours: example of the record of a patient where the overall tumour activity was low.

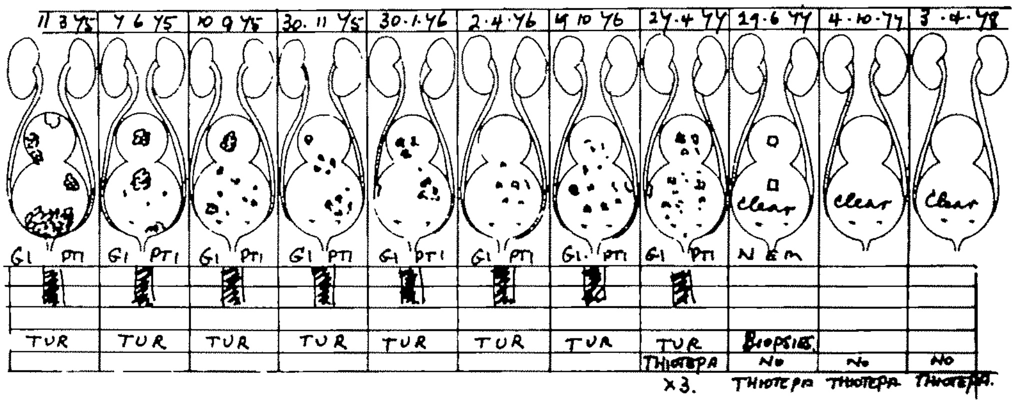

Fig. 2 Multiple new T1 bladder tumours: example of high activity bladder with many new tumours at every cystoscopy.

patient's life at increased risk can be termed disease progression. The biggest single item was bladder muscle invasion but the majority of deaths (60%) were associated with other items of change (Table 4).

It is of note that 9 developed separate invasive tumours from prostatic duct urothelium and the site made for late diagnosis. Six belonged to the high activity group with bladder tumours graded G1 (3), G2 (2) and G3 (1). The last patient grew a similar G3 tumour in the prostate but in all other 5 the prostatic tumours were of a higher grade than those in the bladder, G2 (2) and G3 (3). In the remaining 3 patients all tumours were of G2 grade.

A further 5, all with G1 tumours and all showing persistent high activity, grew urothelial tumours of the upper tracts after 3, 6, 6, 10 and 14 years respectively. Eventually the lesions became bilateral in 2 and 3 patients died from tumours graded G2 and G3 (2)—again an increase in grade over those in the bladder.

Table 4 Disease Progression: Main Change in Disease Status and Turnover Deaths

Main change in status	*Number*	*Deaths*
Grade change to G3, pT1	6	3
Invasion of bladder muscle	32	16
Distant metastases: bladder clear or without change G1 (1); G2 (7); G3 (1)	9	9
Separate invasive urothelial tumour in prostatic ducts	9	9
Urothelial tumour of upper tracts (pelvis (4); ureter (1))	5	3
	61 (18%)	40 (12%)

The 2 factors associated with disease progression and death were a presenting grade of G2 or G3 with subsequent new tumour growth or a persistent high level of tumour neogenesis. One hundred and ten patients displayed one or both of these factors and they accounted for 58 of the 61 progressions and all 40 tumour deaths (Table 5).

The length of time from presentation to progression ranged from 6 months to 16 years with a mean of 4½ years. With increasing tumour grade, time intervals became shorter (Table 6).

Discussion

Only 12% died from bladder cancer, illustrating the low malignant potential of this stage of the disease. During the same period 25% died from unrelated causes and clearly in these age groups other diseases are of more importance as causes of death and morbidity.

Judged by the likelihood of undergoing disease progression and death, only 110 patients (33%) were potentially at serious risk. They were readily identifiable as those presenting with higher grade tumours and growing new ones again after treatment or those exhibiting a continuous high level of new tumour activity. In patients in whom both of these factors were operating the tumour death rate was significantly higher than in those with only one factor involved (Table 7). In the remainder the disease was largely no more than a cause of periodic inconvenience. Among them, the only ones apparently at any degree of risk were a group of 69 who grew G1 multiple new tumours but whose overall activity was low. With only 3 comparatively minor progressions and no tumour deaths the risk has to be considered minimal (Table 7).

Table 5 The Influence of Tumour Grade and Activity on Progression and Deaths

Grade and stage	*Tumour-free*	*New tumour activity*									*Totals*		
		Single tumours			*Multiple tumours*								
					Low activity			*High activity*					
		N	*P*	*D*	*N*	*P*	*D*	*N*	*P*	*D*	*N*	*P*	*D*
G1 pTa	41	38			38	2		18	5	4	135	7	4
pT1	30	15			31	1		29	12	7	105	13	7
G2 pTa	2	1	1	1	1			1			5	1	1
pT1	12	18	11	8	10	6	2	19	12	10	59	29	20
G3 pT1	15	7	6	4	2	1		4	4	4	28	11	8
Totals	100	79	18	13	82	10	2	71	33	25	332	61	40

Of these 2 prognostic factors, raised tumour grade was the more significant (Table 5). A weakness inherent in tumour grading is that it allows for differences in interpretation, so that grade distribution can vary from series to series, making comparisons difficult. Our figure of 28% for grades G2 and G3 combined is appreciably lower than that found in many series where comparable figures commonly ranged from 40 to 55% (Althausen *et al.*, 1976; Gilbert *et al.*, 1978). A conservative attitude towards grading would explain the low figure and this is evidenced by the higher than average correlation rates of 65 and 46% respectively between raised tumour grade and disease progression and death among those seriously at risk.

The second factor associated with a possible unfavourable prognosis, widespread and active tumour neogenesis, is an indication of generalised urothelial instability and the only deaths associated with G1 tumours came from patients in this category (Table 5). Almost certainly the majority of new tumours arise from areas of flat carcinoma *in situ*, hyperplasia or atypia, changes long known to coexist with higher grade tumours (Melicow, 1952) but these changes are commonly found alongside G1 tumours as well (Soloway *et al.*, 1978; Murphy *et al.*, 1979).

A sinister aspect of the condition is that urothelium beyond the bladder may be similarly affected. When bladder lesions were widespread as many as 20% of such patients have been shown to have *in situ* changes in prostatic ducts or urethra (Gowing, 1960; Thelmo *et al.*, 1974), while the

Table 6 Length of Time to Progression by Grade and STage

Time	*G1*		*G2*		*G3*	*Totals*
	PTa	*pT1*	*pTa*	*pT1*	*pT1*	
Within 1 year	2			6	5	13
1 to 2 years		1		10	2	13
2 to 3 years		2		2	1	5
3 to 4 years	1			2	2	5
4 to 5 years	1	1		3	1	6
5 to 10 years	2	8	1	5		16
10 to 16 years	1	1		1		3
Totals	7	13	1	29	11	61
Mean (years)	6	7	7	4	2	4.5

Table 7 Degree of Risk Correlated with Tumour Grade, Activity, Progression and Death

Degree of risk, grade and activity	*Numbers*	*Progressions*		*Deaths*	
Potentially at serious risk					
G1 Grade, continuous high level of tumour neogenesis	47	17	36%	11	23%
G2 G3: new single tumours or multiple ones with low activity	39	25	64%	15	38%
G2 G3: continuous high level of tumour neogenesis	24	16	67%	14	58%
Totals	110	58	53%	40	36%
At minimal risk					
Remaining tumour-free	100				
G1: new single tumours	53				
G1: multiple tumours, low activity	69	3	4%		
Totals	222	3	1%		
Grand totals	332	61	18%	40	12%

reported incidence of ureteric involvement ranges from ·8 to over 50% (Culp *et al.*, 1967; Schade *et al.*, 1971; Skinner *et al.*, 1974). On this evidence it has to be anticipated that a proportion of patients at risk will develop urothelial tumours beyond the bladder, as did 14 in this series. They made up 23% of all progressions and 30% of tumour deaths, while 64% of these tumours were of a higher grade than those in the bladder.

In patients potentially at a higher risk, follow-up, to be adequate, must provide for the monitoring of the whole urothelium. Male patients with widespread tumour neogenesis, together with those in whom the obligatory representative field biopsies show carcinoma *in situ*, should have a resection of prostate. If *in situ* changes are found in the prostatic ducts, cystourethrectomy is the safest course in those fit for operation. Similarly, these patients of both sexes require visualisation of the upper tracts at regular intervals and a biennial intravenous urogram is probably appropriate.

In patients with a higher risk, urine cytology should form part of the routine follow-up, and in our experience it acted as an early warning system, often showing malignant cells in urine long before any tumour was to be seen at cystoscopy or on the urogram.

The clinical course of patients still tumour-free at 5 years indicated that they had a low malignant potential irrespective of presenting tumour grade. With one exception, those growing a first new tumour after 5 years all had single G1 lesions which they faithfully reproduced. These patients are unlikely to come to harm if discharged from routine cystoscopy after 5 years of being tumour-free, particularly if followed thereafter by annual urine cytology. This conclusion is supported by the findings of Newman *et al.* (1980), who showed that in 146 such patients the presenting tumours in 89% had been positive for cell surface A, B or O antigens, indicating a low malignant potential. Tumour grade had been G2 in 52% and G3 in 17%.

The most significant features of the natural history of the T1 bladder tumour may therefore be summarised as follows: The malignant potential and death rate were low, strongly favouring an overall conservative approach to management.

Only a limited number of patients were potentially at serious risk and once they were identified, follow-up could be concentrated on this group. An appreciable proportion of those at risk developed urothelial tumours beyond the bladder, stressing the need to monitor the whole urothelium in these patients. The majority of these tumours were of a higher grade than those found in the bladder.

In patients tumour-free after 5 years the natural history suggested that a reasonable and safe course was to discontinue routine cystoscopy after that time and to continue supervision by urine cytology.

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Radiotherapy and Cystectomy for T3 Bladder Carcinoma

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Summary—The survival of 102 patients with category T3 transitional cell carcinoma of the bladder treated by pre-operative radiotherapy and radical cystectomy has been analysed according to the degree of down-staging of tumour as assessed by the depth of infiltration of cancer in the operative specimen. Five-year survival was 60% for patients showing evidence of down-staging compared with 30% when persistent deeply invasive tumour was present at the time of cystectomy.

Analysis of available data suggests that survival of patients with category T3 bladder cancer is determined by the response of the tumour to initial radiotherapy rather than the dose of radiotherapy or the addition of cystectomy. Despite radical treatment, the survival of patients with locally advanced bladder cancer is poor; alternative, more effective forms of therapy should be sought.

In the treatment of invasive bladder carcinoma with pre-operative radiation and cystectomy it is claimed that the improvement in survival achieved by the addition of pre-operative radiation (Whitmore, 1980) results from the sterilisation of microscopic metastases in the pelvic lymph nodes and soft tissues that would be left untreated by cystectomy alone. It is also possible that pre-operative radiation prevents the dissemination of viable malignant cells during cystectomy.

Werf-Messing (1979) demonstrated that the patients whose tumours had responded to radiotherapy at the time of cystectomy survived much better than patients with persistent deeply invasive tumour in their operative specimen. Blandy *et al.* (1980), employing radical radiotherapy alone as primary treatment, reported a similar difference in survival.

Patients and Methods

Category T3 transitional cell carcinoma of the bladder has been treated in Newcastle upon Tyne by pre-operative radiotherapy and radical cystectomy with ileal conduit urinary diversion. All patients were assessed clinically by cystoscopy, bimanual examination and resection biopsy under general anaesthesia and histological evidence of muscle invasion of the bladder wall obtained in the majority of patients. No attempt was made to resect all exophytic tumour before commencing radiotherapy. Radiotherapy comprised 4000 to 4500 rads given in 4 to 4½ weeks by anterior, posterior, right and left lateral fields to the deep pelvis, including bladder, tumour and regional lymph nodes. Radical cystectomy was performed 1 to 6 weeks after completing radiation.

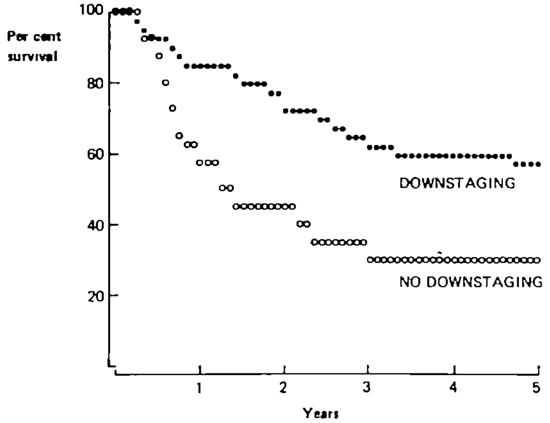

Fig. 1 Five-year survival for category T3 transitional cell carcinoma of the bladder treated by pre-operative radiotherapy and cystectomy: comparison of patients showing evidence of down-staging of tumour at time of cystectomy with persistence of invasive cancer.

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

The survival of 102 consecutive patients treated in the above manner has been analysed according to the extent of down-staging of the tumour in response to radiotherapy as measured by the depth of infiltration of tumour in the cystectomy specimen. The data have been analysed using the methods of Peto *et al.* (1976) with extensions to allow for the presence of possible prognostic factors. An additional 6 patients who died of treatment complications (operative mortality 5.5%) were excluded from this analysis but are included in later tables for comparison with results from other publications.

Results

Five-year survival for patients showing a reduction of their tumour after pre-operative radiation was 60% compared with 30% for patients with tumour continuing to infiltrate deep muscle in the cystectomy specimen (Fig. 1). This difference was significant and confirms the observation of previous authors that survival is doubled for patients with little or no residual tumour at the time of cystectomy: 35% of patients had no residual tumour in the operative specimen (P0) and a further 39% had only superficial tumour (Pis-P2). Improvement in survival was proportional to the degree of down-staging of tumour, patients with no residual tumour having the best survival. The response to radiotherapy was not related to tumour grade, a similar proportion of well differentiated and poorly differentiated tumours being down-staged.

It has been suggested that the apparent down-staging of bladder tumours following pre-operative radiotherapy may be due to over-staging before treatment and the inclusion of some patients with category T1 or T2 disease. Table 1 shows that biopsy proof of muscle invasion was obtained prior to commencing treatment in 74% of patients showing subsequent down-staging compared with 78% showing no response to radiation. There is a similar small difference in the data from Rotterdam (Werf-Messing, 1979). Figure 2 compares the survival of patients whose pre-treatment biopsies confirmed the presence of muscle invasion (pT2/3) with those where muscle infiltration was not demonstrated or not assessable (pTX). It is clear that there was no advantage for the latter group and that the possible inclusion of a few over-staged tumours did not account for the overall differences in survival observed.

Table 1 Proportion of Patients With Clinical Category T3 Bladder Cancer With Pre-treatment Biopsy Proof of Muscle Invasion Versus Subsequent Response to Pre-operative Radiotherapy

	Down-staging	*No down-staging*
Newcastle	74%	78%
Rotterdam	67%	74%

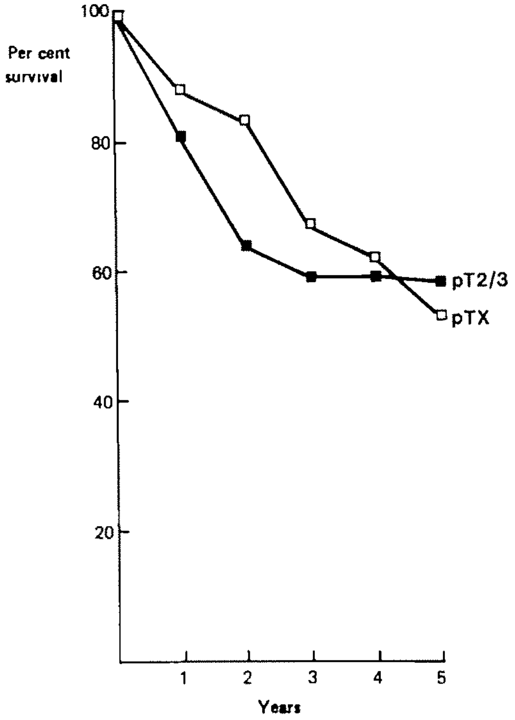

Fig. 2 Five-year survival in patients with pre-treatment biopsy proof of muscle invasion (pT2/3) compared with patients with inadequate pre-treatment biopsy (pTX).

Discussion

The results from various centres employing radical radiotherapy alone or combination treatment are remarkably similar. Table 2 summarises the proportion of patients responding to pre-operative radiotherapy and shows that this was "complete" in 30 to 40% of patients in all series and was the same for both pre-operative radiotherapy and radical radiotherapy. This implies that there are 2 different bladder tumour populations (Blandy *et al.*, 1980), that are distinguished by their sensitivity to radiotherapy. This distinction is evident after only 4000 rads in 4 weeks and is

Table 2 Incidence of "Complete" and Partial Regression Following Radical Radiotherapy (*) or Pre-operative Radiation as Assessed by Post-treatment Cystoscopy or Pathological Examination of Cystectomy Specimen

	"Complete" regression	*Partial regression*	*No change*
Blandy (1980)*	42%	25%	33%
Hall	35%	39%	26%
Werf-Messing (1979)	30%	39%	31%
Wallace and Bloom (1976)	29%	17%	54%
Miller (1977)	29%	—	—
Prout (1973)	33%	34%	33%

maintained at higher radiation dosage. The difference does not depend upon tumour grade, nor is there any other clinical or histological feature which enables us to predict which tumour will respond.

Table 3 summarises 5-year survival data according to the down-staging of tumour following radical radiotherapy (Blandy *et al.*, 1980) and combination treatment (Prout *et al.*, 1973; Wallace and Bloom, 1976; Miller, 1977; Werf-Messing, 1979). The large difference in survival between patients showing evidence of down-staging (51-61%) and no down-staging (17-29%) suggests that survival is determined by the initial response to radiotherapy rather than the total dose of radiation given or the addition of radical cystectomy. However, the apparent complete disappearance of tumour at endoscopic assessment after radical radiotherapy does not preclude recurrence of disease and unfortunately one-third of such tumours recur if the bladder is not removed. Similarly after cystectomy some patients still develop local and/or distant metastases despite an apparently complete response to pre-operative radiation.

Table 3 Down-staging of T3 Bladder Cancer: 5-year Survival Versus Response to Radiotherapy (*Radical Radiotherapy)

	Down-staging	*No down-staging*
Blandy (1980)*	56%	17%
Hall	55%	25%
Werf-Messing (1979)	61%	25%
Wallace and Bloom (1976)	55%	22%
Miller (1977)	54%	25%
Prout (1973)	51%	29%

There has been considerable discussion in recent years concerning the merit of one form of treatment or another for locally advanced bladder cancer with marked polarisation of opinions in different urological units. Table 4 summarises published results, comparing radical radiotherapy alone with radiotherapy and cystectomy. The results of only 2 randomised prospective trials are available. Wallace and Bloom (1976) reported a small advantage not amounting to statistical significance for combined treatment which, in particular, was not observed in elderly patients. Miller (1977) reported significantly better survival following combination treatment but the number of patients studied was small.

Comparisons between different centres must be made with caution but it is striking that the differences in survival are related to the behaviour of tumour in response to radiation rather than the particular treatment employed. In view of this, the decision to employ one form of therapy rather than another cannot be based upon the likelihood of cure and it should be recognised that the choice depends much more upon subjective factors such as the urologist's personal preference and his or her impression of the likely quality of the patient's survival. The disadvantages of cystectomy are the operative mortality, the cost of hospital care for major surgery, the incidence of late treatment complications and the necessity for permanent urinary diversion. The disadvantages of radiotherapy are the treatment morbidity, late treatment complications, some of which can be fatal, and the fact that non-

Table 4 Five-year Survival of Patients with Category T3 Transitional Cell Carcinoma of the Bladder Treated by Radical Radiotherapy Versus Radiotherapy and Cystectomy

Radiotherapy	*Per cent survival*	*R.T. + cystectomy*
	46	Miller (1977)
	45	Werf-Messing (1979)
Blandy *et al.* (1980)	38	
	35	Hall
	34.5	Reid *et al.* (1976)
	33	Wallace and Bloom (1976)
Goffinet *et al.* (1975)	28	
Wallace and Bloom (1976)	21	
Miller (1977)	16	

survivors suffer the symptoms of recurrent local cancer.

It is suggested that further argument between those who favour radiotherapy or combination treatment is likely to be unproductive and it should be recognised that both forms of therapy are equally ineffective. Urologically speaking, the patient's most precious possession is his bladder and it should not be removed or irradiated without good cause. Rather than expend further energy on internecine discussion we should combine our efforts in seeking an alternative, more effective form of treatment for infiltrating bladder cancer.

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Occupational Bladder Cancer and Cigarette Smoking in West Yorkshire

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Summary—This paper reports the preliminary findings of a case-controlled study of bladder cancer in parts of West Yorkshire. The first 991 cases have been analysed and the results of the occupational exposure for 5 occupations are reported.

There is an increased risk of bladder cancer associated with smoking cigarettes in both males and females. These results take both the age and the year of diagnosis into account and are statistically significant. Chemical industry workers and printers have been shown statistically to have a high risk ratio, whereas leather workers, hairdressers and dye-users have a statistically insignificant risk ratio. For process workers in the dye manufacturing industry the length of service is significantly correlated with the risk of bladder cancer and so is the age at which a man first becomes a process worker.

Many epidemiological studies have shown that bladder cancer cases are associated with a range of industrial processes which bring workmen into contact with specific carcinogens. The bladder carcinogens include 2-naphthylamine and benzidine and have caused bladder cancer in the dye manufacturing industry (Case, 1953), the rubber and cable making industries (Davies, 1965; Case, 1966), and the coal gas and coke industries (Doll *et al.*, 1965). Many other trades and professions have also been suggested as producing excess bladder cancer cases amongst their workforces (Anthony and Thomas, 1970; Cole *et al.*, 1972). It is the purpose of this report to introduce the preliminary results from a study in Yorkshire. Results which confirm one established risk-occupation are presented together with data which throw suspicion on some other occupations.

Methods

All patients with bladder cancer presenting in 3 Yorkshire centres (Bradford, Huddersfield and Wakefield) over a 3-year period were interviewed for a wide range of information including cigarette smoking habits and a full occupational history of all work undertaken by each patient since leaving school. In addition, an age and sex matched comparison group without malignant disease was also interviewed using the same questionnaire. The information collected is shown in Table 1.

Table 1 Information Collected

Identification
Coffee and alcohol drinking habits
Saccharin use
Smoking habits
Past medical history
Past drug treatment
Occupational history
Hobbies
Family history

The analysis of the data is based on comparing the responses of the cases with those of the controls. Thus risk ratios, confidence limits and tests of significance based on the approach of Mantel and Haenszel (1959) and Miettinen (1976) can be computed. This method allows several factors to

Table 2 West Yorkshire Bladder Cancer Epidemiological Study

	Cases	*Comparison group*
Old cases		
Males	472	468
Females	153	156
New cases		
Males	272	525
Females	94	189

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 3 Risks Associated with Cigarette Smoking Adjusted for Age and Year of Diagnosis

	Risk ratio	*95 per cent confidence limits*
Current smokers		
Male	1.8	1.5-2.3
Female	1.6	1.1-2 2

be taken into account and it is possible to compute chi-values which measure the heterogeneity of such estimates.

Results

This preliminary report gives results from an analysis of the first 744 male and 247 female cases interviewed compared with groups of 993 and 345 controls respectively. There were more interviews in the comparison group because new cases have 2 matched patients to one for old cases (Table 2).

Table 3 indicates that an increased risk of bladder cancer is associated with smoking cigarettes and this holds true for both sexes, although the risk is slightly greater in males (1.8) than females (1.6). Both results take age and the year of diagnosis into account and are statistically significant.

Several occupations were examined for possible risks. These were selected on the basis of previous work. The results, which take account of sex, age and year of diagnosis, are summarised in Table 4 as risk ratios with their 95% confidence limits. The statistically insignificant risk ratios for leather workers, hairdressers and dye-users are shown in parentheses.

The workers in the chemical industry are a heterogeneous group (Table 4) but for dye manufacturing process workers alone the risk ratio amounts to 3.5 (2.2-5.3).

Table 5 refers to the effect cigarette smoking has upon men in certain occupations where the risk for non-smoking workers is compared with the risk for those who smoke. Non-significant results are given in parentheses. The significance (S) or non-significance (NS) refers to the estimates of risk between smokers and non-smokers.

Table 4 Occupational Risks (Summary Table)

	Risk ratio	*95 per cent confidence limits*
Chemical industry workers	2.9	2.0-4.3
Leather workers	(1.2)	0.5-3.1
Hairdressers	(0.9)	0.3-3.2
Printers	3.1	1.4-6.8
Dye users	(1.3)	0.8-2.4

Table 5 Effects of Cigarette Smoking

	Risk ratios smokers	*Non-smokers*	
Dye manufacture process workers	4.6	(1.9)	S
Printers	3.6	(2.3)	NS
Dye users	(1.2)	(0.4)	NS

Further investigations on the process workers in the dye manufacturing industry reveal that the length of service is correlated significantly with the risk of bladder cancer (Table 6). The age at which a man first becomes a process worker also appears to be significant (Table 7) and the rates range from 7.3 in the youngest worker to 1.0 in those 40 years and older.

Discussion

This report deals specifically with the risks of bladder cancer associated with 5 occupations (Anthony and Thomas, 1970; Cole *et al.*, 1972).

It is not surprising to find that dye manufacturing process workers have the highest risk because previous studies by Case (1953) and others showed it to be due to the exposure of such workmen to benzidene and naphthylamine. Of greater interest are the observations made in Tables 6 and 7, which show "dose-response" relationships with length of service and with age at first employment. These 2 features are slightly correlated but nevertheless the observations that length of exposure is of significance in these workers is a new finding. The fact that workers who were over 40 when they first started in the industry apparently

Table 6 Length of Employment of Process Workers in the Dye Manufacturing Industry

Years employment	*Standardised rate ratios*
<10	1.7
10-29	8.5
>29	10.5

Chi (M-H) = 5.1, $P = 0.001$.

Table 7 Age at Starting Work in the Dye Manufacturing Industry

Age	*Standardised rate ratios*
Under 30	7.3
30-39	5.2
Over 39	1 0

Chi (M-H) = 3.5, $P = < 0.001$.

have no risk, despite known exposure, is of particular interest. Does this mean that the biological susceptibility of cells changes with age, or did these older workers behave differently in the factory environment?

The observations on smoking habits in dye process workers are also unique. The data suggest that whereas cigarette smoking dye workers have an increased risk of bladder cancer, non-smokers have virtually no risk.

Printers were thought to be at risk because of their exposure to ink fly (Young and Russell, 1926) but this has not been demonstrated since, perhaps because of the high rate of lung cancer among printers (Cole *et al.*, 1972). These results are of some significance partly because it was thought that printers' inks contained variable amounts of carcinogenic substances, including the benzpyrene derivatives. The preponderance of lung cancer in printers was thought to be due to their smoking habits, which might also be of relevance with respect to bladder cancer. There proved to be very few non-smoking printers but, despite this, the figures show that for printers who smoke the risks are increased and for those who do not the values are non-significant (Table 5). The numbers, however, are too small to indicate exactly what influence smoking has in print workers.

Leather workers and shoemakers have been implicated in several studies (Lockwood, 1961; Wynder *et al.*, 1963), but this study does not show an increased risk for these workers.

Hairdressers using hair-dyes have been suggested as being at risk by Dunham *et al.* (1968) but this has not been substantiated by this study.

Dye users have been implicated as a risk occupation by Anthony and Thomas (1970) and obliquely by Wynder *et al.* (1963) but this study does not substantiate these results. This may be because in the woollen and worsted trades in Yorkshire they handle only diluted, wet dyestuffs and not the powdered form which the dye process workers produced.

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Transitional Cell Carcinoma Involving the Prostate

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Summary—Transitional cell carcinoma involving the prostate gland was studied in 27 patients. Three different groups were recognised on the basis of the clinical pattern and histological findings. Each group has a different prognosis and merits a different approach to treatment. Thus, stromal involvement of the prostate by transitional cell carcinoma is a sinister finding that requires radical treatment, whereas ductal involvement by either carcinoma *in situ* or non-invasive papillary tumours can be managed less aggressively. This study emphasises that the present classification for these tumours is unsatisfactory and that adequate histopathological information is essential for their management.

Involvement of the prostate by urothelial carcinoma is generally taken to mean an invasive tumour infiltrating the prostate (*i.e.* pT4a). However, there are other patterns of involvement of the prostatic urethra, ducts and glandular stroma by transitional cell carcinoma. *In situ* carcinoma of the prostatic ducts with similar involvement of the prostatic urethra and bladder was described 29 years ago (Melicow and Hollowell, 1952; Ortega *et al.*, 1953) and the significance of this finding has been discussed recently (Thelmo *et al.*, 1974; Seemayer *et al.*, 1975).

Subsequently, *in situ* and invasive transitional cell carcinoma of the prostate originating in the ducts surrounding the prostatic urethra and not associated with bladder tumours has been reported (Ende *et al.*, 1963; Ullmann and Ross, 1967; Karpas and Moumgis, 1969; Kopelson *et al.*, 1978; Kirk *et al.*, 1979; Wolfe and Lloyd-Davies, 1981). Schellhammer *et al.* (1977) have made a study of the entire spectrum of histological patterns based on their retrospective analysis of 38 cystectomy specimens where the prostate was involved, although in half of the patients there was no pre-operative indication by cystoscopy of a prostatic urethral abnormality.

In an attempt to clarify the terminology and nature of this disease, we have studied 27 patients in whom the prostate was involved by a urothelial carcinoma.

Patients and Methods

All patients presenting during the past 3 years with histologically proven involvement of the prostate by a transitional cell carcinoma were reviewed. All but one patient first presented during this period; this patient was found to have transitional cell carcinoma involving the prostate in 1973 and has since had recurrences in the prostatic urethra on numerous occasions. Seven of the 27 patients had previously detected bladder tumours; the remaining 20 were new cases. The histology in all 27 patients has been reviewed by the same pathologist (M.A.M.).

Classification

Three identifiable sub-groups were apparent:

1. Carcinoma *in situ,* involving prostatic urethra and ducts with or without similar bladder involvement.
2. Non-invasive papillary tumour of prostatic urothelium and major ducts together with similar bladder tumours.
3. Invasive tumours of bladder base and neck with extension into the prostate.

Results

Group 1 (5 patients)

All patients in this group presented with symptoms of frequency and dysuria and on cystoscopy showed appearances ranging from apparently

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

normal urothelium to widespread patchy erythema. In 2 cases, bladder and prostatic urothelium appeared normal and the diagnosis was made incidentally when TUR chips were examined.

Histology of the bladder and prostatic urothelium showed bizarre hyperchromatic cells with increased nucleo-cytoplasmic ratios and a tendency to exfoliate (Fig. 1), resulting in a high incidence of positive urinary cytology. The major prostatic ducts showed similar cells, but there was no involvement of the stroma of the prostate (Fig. 2).

In view of carcinoma *in situ* deep down within prostatic ducts, we felt that a surface-acting chemotherapeutic agent would not be effective and hence chose to treat 3 of the patients in this group with *systemic* chemotherapy. Of the remaining 2, one has received palliative radiotherapy to an area of metastases and the other is under observation following transurethral resection of the prostate, since there is no further evidence of carcinoma *in situ* in the bladder. In 4 of the 5 patients the disease has shown no progression and one has developed a metastasis.

Group 2 (10 patients)

This group consisted of 10 patients with non-invasive papillary tumours of the prostatic urethra and ducts which accompanied similar tumours of the bladder urothelium either synchronously or at different points in time. In 3 cases the prostatic involvement was detected synchronously with bladder tumour. In the remaining 7 cases there was an interval ranging from 13 months to 10 years between detection of bladder tumour and the diagnosis of prostatic involvement. The symptom at presentation in all cases was haematuria, often accompanied by dysuria. At cystoscopy there was a papillary tumour in the prostatic urethra which was TUR biopsied.

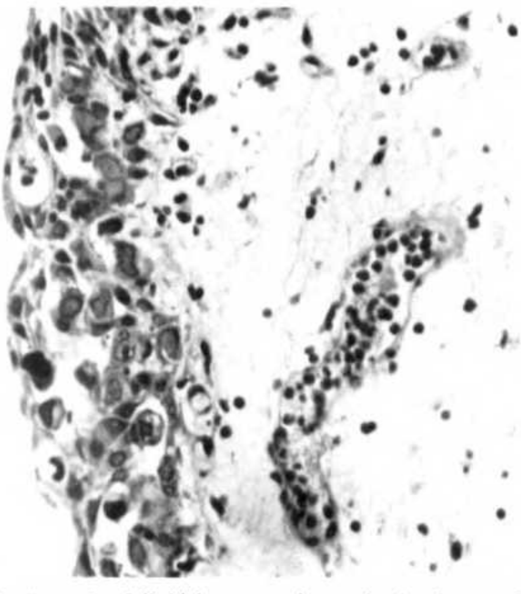

Fig. 1 Group 1—full-thickness, carcinoma *in situ* change of the prostatic urothelium (H and E × 300).

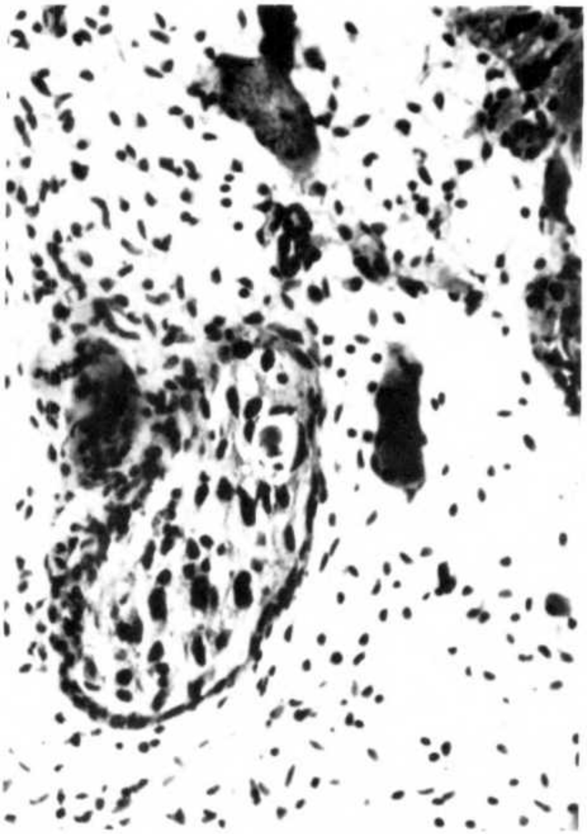

Fig. 2 Group 1—carcinoma *in situ* within periurethral ducts (H and E × 300).

Histology of the prostatic lesions showed superficial tumour involving the prostatic urothelium, growing down into and often packing the major prostatic ducts (Fig. 3). There was no involvement of the prostatic stroma. Most of these tumours were moderately to well differentiated at the time of detection (G1 in 6, G2 in 2 and G3 in 2).

All of these patients were managed initially by endoscopic resection and diathermy. One of them had received a course of radical radio-

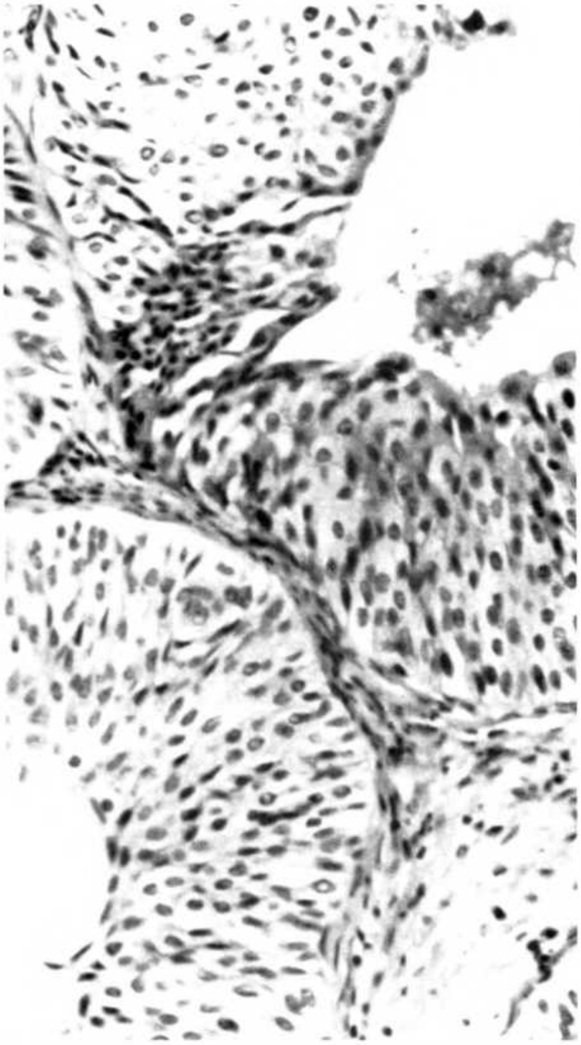

Fig. 3 Group 2—Grade 1, urothelial tumour packing the prostatic ducts (H and E × 300).

therapy 6 years previously but continues even now to produce papillary tumours in the bladder and prostate; he has been managed successfully by endoscopic means.

Three patients in this group have also received intravesical chemotherapy in an attempt to control the frequent and florid bladder recurrences.

In 6 of these patients the disease remains under control by endoscopic means. In 2 patients the tumour in the prostate was upgraded and in 2 patients (one of whom is common to the previous 2) there have appeared areas of microinvasion of the stroma. The remaining patient, who had papillomatosis of the bladder beyond adequate endoscopic control, was advised to have a cystectomy but refused.

Group 3 (12 patients)

Most of these patients presented with symptoms of bladder outlet obstruction with or without haematuria. At cystoscopy all were found to have invasive tumours (into muscle) involving the bladder base and neck region. The prostate was contiguously infiltrated in all cases.

Histological examination of the prostatic lesions showed poorly differentiated (G3) tumour in all cases. The pattern changed from mainly ductal involvement (Fig. 4) to varying degrees of stromal invasion of the prostate, *i.e.* from circumscribed areas in some cases to total obliteration of prostatic architecture in others (Fig. 5). In 2 cases there was stromal invasion of the prostate without involvement of major prostatic ducts (Fig. 6). This could be secondary to direct extension of the bladder tumour through the bladder neck muscle into the body of the prostate.

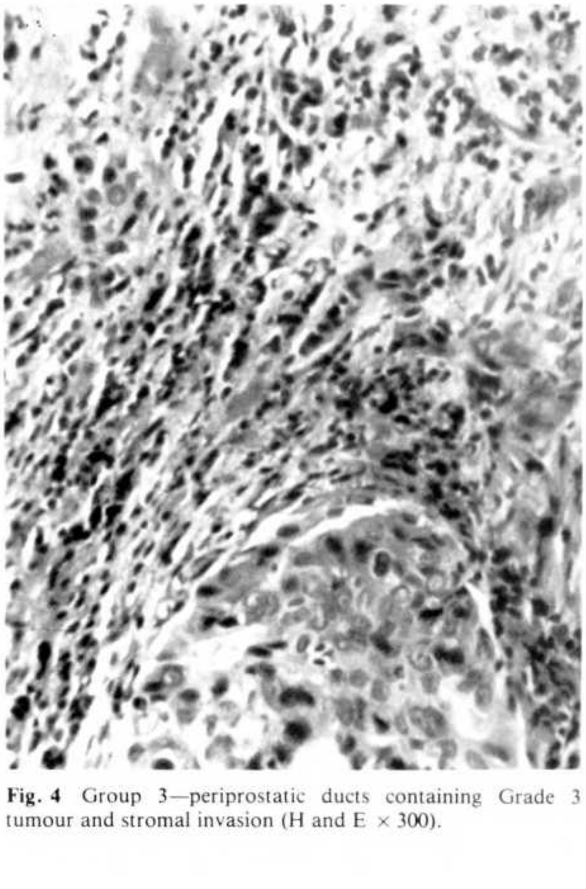

Fig. 4 Group 3—periprostatic ducts containing Grade 3 tumour and stromal invasion (H and E × 300).

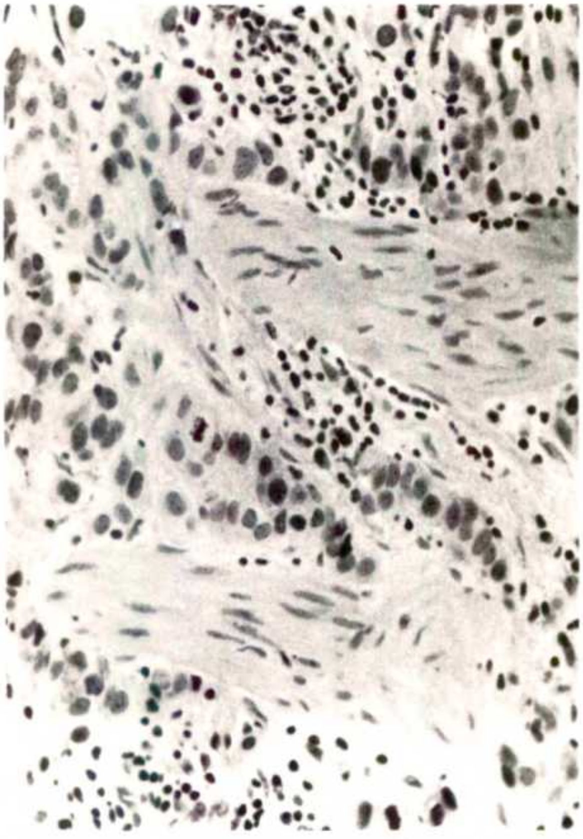

Fig. 5 Group 3—complete replacement of prostatic architecture by Grade 3 urothelial tumour (H and E × 300).

Ten patients had radical radiotherapy and 2 of these later had a salvage cystourethrectomy and adjuvant chemotherapy. Two patients presented with metastases and had palliative radiotherapy alone. Of the 12 patients in this group 3 are alive and may be presumed to be free of disease (35 months, 21 months and 6 months following their detection). Five patients have died (within 1, 1, 5, 11 and 13 months) and 3 are alive with evidence of metastases or residual urothelial tumour.

Discussion

The findings in this study emphasise that prostatic involvement by a urothelial carcinoma is not a single pathological entity. The UICC (1978) classification is not sufficiently descriptive to include the different types of this disease. It has been our practice to take generous TUR biopsies of the prostatic urethra in all patients with visible tumour in this area, and also in patients with evidence of flat *in situ* carcinoma of the bladder.

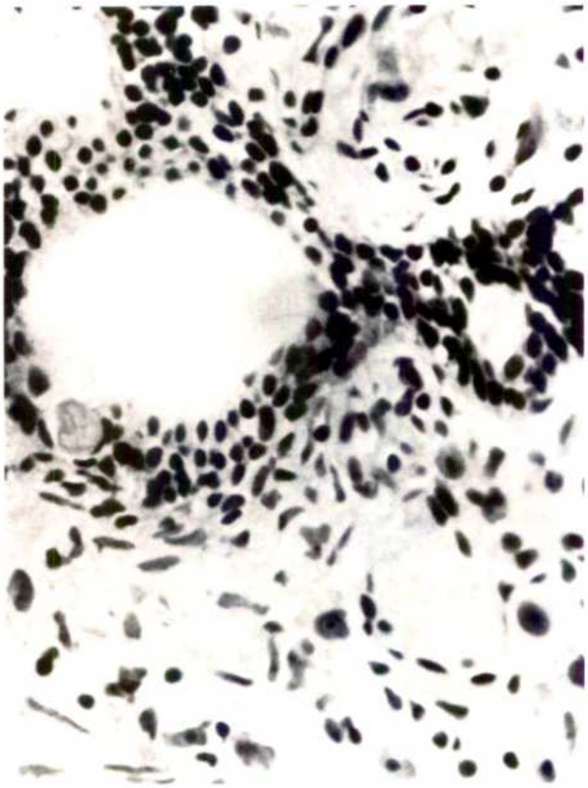

Fig. 6 Group 3—stromal invasion by Grade 3 urothelial carcinoma in the absence of ductal involvement (H and E × 480).

The grade of the tumour and the extent of prostatic involvement can then be noted in the urothelium, major ducts and stroma. This information is sufficient to classify the prostatic tumour into one of the 3 groups described herein.

The number of patients in this study is too small and the time interval not long enough to make any firm conclusions regarding prognosis or optimum treatment. However, some general trends are apparent.

The exact incidence of transitional carcinoma involving the prostate gland remains uncertain but is probably greater than suspected. Ende *et al.* (1963) suggested that 1 to 4% of all primary prostatic carcinomas were urothelial in origin. Wolfe and Lloyd-Davies (1981) suggested this figure was too low and that the condition was probably under-reported. We would agree with this; the condition had scarcely been reported in this pathology department prior to a change in biopsy policy and the more ready resectoscopic sampling of the prostate by the urologists introduced 4 years ago.

Our experience differs from some of the earlier series where all of the cases were put together and it more closely resembles that reported by Kirk *et al.* (1979), who demonstrated the need to subdivide these cases on the basis of pathological findings.

Non-invasive papillary tumours do not share the label of poor prognosis given generally to urothelial tumours of the prostate. It appears that they can be treated endoscopically provided they are low grade and confined to the prostatic ducts. However, these cases need careful observation because the grade of the tumour in the ducts can worsen, with the tumour becoming invasive. When this does occur, radical treatment using either radiotherapy, surgery or a combination of both is recommended (Johnson *et al.*, 1972).

A high proportion of cases with flat carcinoma *in situ* of the bladder show a similar involvement of the prostatic urethra and ducts (Seemayer *et al.*, 1975) and TUR biopsies of the prostatic urethra are necessary in such cases. A positive biopsy in our opinion contraindicates intravesical chemotherapy.

Our experience with invasive tumours of the bladder base and neck which have contiguously involved the prostate (*i.e.* pT4a) is in keeping with that of numerous other workers, starting with Whitmore and Marshall who, in 1962, noted that this sinister finding generally implied a dire outlook for the patient.

It is concluded that transitional cell carcinoma involving the prostate does not necessarily carry a poor prognosis. These tumours need to be described in greater morphological and histological detail on the basis of an adequate TUR biopsy. Only then can the exact patterns of management and prognosis be described accurately.

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Transitional Cell Carcinoma Involving the Prostate—An Unfavourable Prognostic Sign in the Management of Bladder Cancer?

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Summary—Among 38 male patients undergoing cystectomy for bladder carcinoma, invasion of the prostate, or coincident dysplasia or carcinoma of the prostatic ducts was found in 21. It is suggested that these changes confer a poor prognosis with regard both to response to non-operative treatment and to survival following cystectomy.

A previous communication on transitional cell carcinoma involving the prostate diagnosed by transurethral surgery noted that in some patients with apparent primary prostatic transitional cell tumour there was evidence of carcinoma *in situ* elsewhere in the urothelium (Kirk *et al.*, 1979). The present paper explores further the relationship between transitional cell tumours of bladder and prostate and discusses its prognostic significance.

Patients and Methods

Of 53 men undergoing total cystectomy for bladder carcinoma between 1973 and 1980, histological sections of the prostate were available for retrospective study from 38. These sections have been reviewed by 2 of us (A.S. and B.E.G.) and the results correlated with the clinical progress of the patients.

Results

The mean age of the 38 patients was 65 years (range 43-77). Except for one man with carcinoma *in situ* without discrete tumour, all presented with overt bladder carcinoma. Usually there was no clinical suspicion of prostatic pathology. In most cases cystectomy was a salvage procedure. Thirty-three patients had received radical radiotherapy. Relevant abnormalities (benign hypertrophy being counted as "normal" for the purposes of this study) were found in 21 of the prostates (Table 1).

Prostatic Duct Pathology

In those cases classified as "dysplasia" (Fig. 1) the prostatic duct epithelium showed hyperplasia and cellular atypia, but this was insufficient to be considered frankly neoplastic (Ullman and Ross, 1967). Frank transitional cell carcinoma of the ducts occurred as carcinoma *in situ* in 6 and as invasive tumour in 4 patients (Fig. 2).

Invasion by Contiguous Bladder Tumour

Of the 3 patients in whom the prostate was directly invaded by the bladder tumour, one had prostatic duct dysplasia in addition but is classified under "invasion" in Tables 2 and 3. The other 2 had normal glands.

Adenocarcinoma

In one patient (who died 10 days after his cystectomy) a previous extensive transurethral resection and prolonged oestrogen therapy made prostatic histology difficult to interpret. The other man had, in addition, prostatic duct transitional cell carcinoma and is classified as such in Tables 2 and 3. Adenocarcinoma was not considered an abnormality relevant to the present study and

Table 1 Prostatic Pathology in 38 Patients (2 Patients with Double Pathology)

Normal (including BPH)	16
Adenocarcinoma	2
Invasion (one prostate with duct dysplasia)	3
Dysplasia	9
Duct TCC (one prostate also adenocarcinoma)	10

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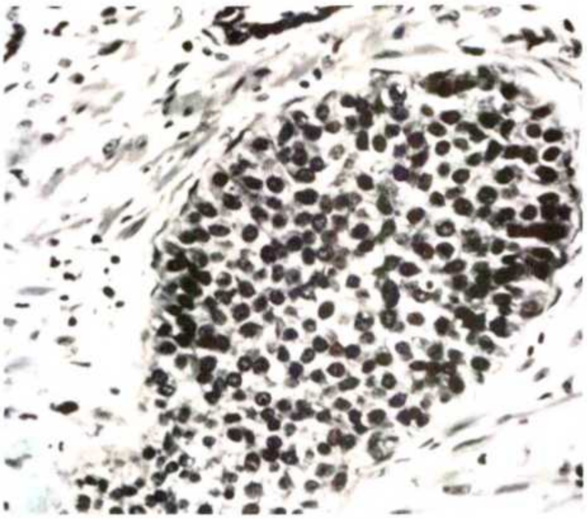

Fig. 1 Prostatic duct—dysplasia (×254).

therefore the first patient was not included in the 21 classed as having "abnormal" glands.

Histology of the Bladder Tumours (Table 2)

The grading of tumours was based on the principles adopted by the Bristol Bladder Tumour Registry (Miller *et al.*, 1969). Incomplete information in some of the case records prevented full assessment of the stage of the tumour. The distinction between "superficial" and "invasive" (which in this context indicates invasion of bladder muscle) was made on the basis of both clinical and histological data. When the tumour in the cystectomy specimen was compared with the original, in a number of patients there had been a clear histopathological deterioration as indicated in the table.

Table 2 Pathology of Associated Bladder Tumour

	Prostate			
	Normal	*Invasion*	*Dysplasia*	*Duct TCC*
Original bladder tumour				
Low grade	2	0	1	2*
Average grade	6	2	5	4
High grade	8	1	1	3
Carcinoma *in situ*	0	0	1	4†
Superficial	6	0	1	3*
Invasive	10	3	7	7
Cystectomy tumour higher grade	3	0	5	1
Superficial tumour becoming invasive	1	0	1	1

* Includes one patient with long history of low grade superficial tumour, developing high grade invasive lesion prior to cystectomy.

† Includes one patient with carcinoma *in situ* only.

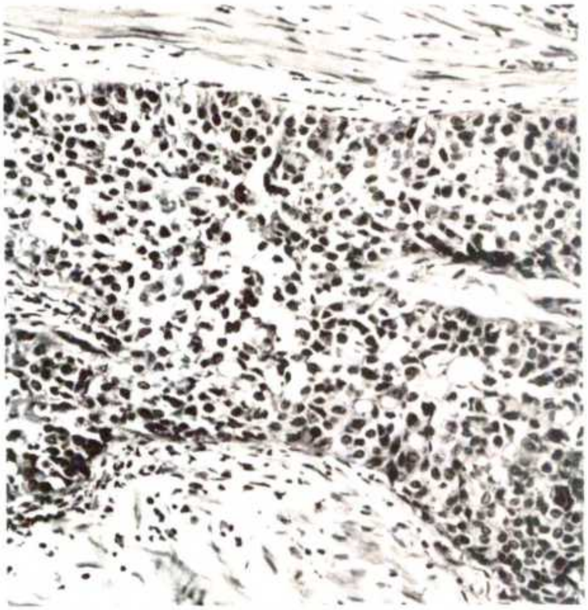

Fig. 2 Prostatic duct—transitional cell carcinoma *in situ* (×159).

Clinical Progress (Table 3)

The mean length of history prior to cystectomy was similar in all groups. In calculating the mean for the ductal transitional cell carcinoma group, one man with a 32-year history of recurrent low grade tumours was excluded, since the high grade invasive tumour which developed shortly before his cystectomy seemed to be a new event. All 3 patients with prostates invaded by bladder tumour died within one year of cystectomy. All but one

Table 3 Clinical Progress of Patients

	Prostate			
	Normal	*Invasion*	*Dysplasia*	*Duct TCC*
Mean history prior to cystectomy (months)	27	38	30	23*
Operative deaths†	2	0	0	1
Alive	8	0	4	1
Death—from tumour	5	3	3	7
other causes	1	0	0	1
Lost to follow-up	0	0	1	0

* Mean excludes one patient with 32-year history.

† Man with adenocarcinoma was operative death: not included in table.

of the deaths of the patients with ductal transitional cell carcinoma occurred within 2 years.

Discussion

In Bristol cystectomy is normally used as a salvage procedure when other treatments have been exhausted. A study of the Bristol cystectomy patients might therefore show common features which augur a poor response to radiotherapy (and other non-operative treatment). In these men, prostatic changes as described occurred in 21/38 patients (the man with only adenocarcinoma being excluded). This compares with an incidence of 42/350 in a series from a centre where elective cystectomy is practised (Schellhammer *et al.*, 1977). Thus the presence of abnormalities in the prostatic ducts might prove to be a factor predicting that a patient will have a greater chance of coming to salvage cystectomy. It was also found (Table 2) that although the patients with duct dysplasia as a group tended to have pathologically more favourable tumours at the outset, in 5 of them a clear deterioration in tumour grade had occurred by the time of cystectomy. However, information was available only about the state of the prostate *at the time of cystectomy*, and it is impossible to know whether the changes found were present earlier in the course of the patients' disease. Thus duct pathology might develop *as a late change* in those who respond poorly to radiotherapy rather than be predictive of this poor response. It is even possible that the changes found could be a pathological response of the prostate to the radiotherapy which the majority of patients had received.

In view of the previous findings (Kirk *et al.*, 1979) that there was an apparent association between prostatic transitional cell tumours and carcinoma *in situ* in the bladder and elsewhere, it is of interest to note that carcinoma *in situ* was present in the bladder of one patient with dysplastic prostatic ducts and in at least 4 of those with ductal carcinoma. One of the latter never developed frank bladder tumour, although the carcinoma *in situ* itself was a source of severe symptoms.

It is recognised that invasion of the prostate by a bladder tumour confers a poor prognosis (Whitmore and Marshall, 1962) and it was no surprise to discover the early deaths of the 3 patients in this group (Table 3). In the previous study (Kirk *et al.*, 1979), patients with primary transitional cell carcinoma of the prostatic ducts rarely survived longer than 2 years. A similar prognosis seems to apply when such prostatic pathology is found at cystectomy performed for bladder tumour (Table 3). Although patients with dysplasia may do better, it should be noted that 2 of the survivors were within one year of their cystectomy at the time of writing.

Accepting the limitations of a retrospective study, we have demonstrated the clear possibility that prostatic duct carcinoma and dysplasia in association with a bladder tumour have a prognostic significance. A prospective study now seems desirable to determine whether prostatic biopsy would be a useful addition to the assessment of a bladder carcinoma in a male patient, and whether the information from such a biopsy would be helpful in the subsequent management of the patient.

Acknowledgements

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The Natural History of Untreated "Prostatism"

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Summary—One hundred and seven patients with symptoms of prostatic obstruction in whom prostatectomy was not clinically indicated were reviewed after an interval of 5 years. Ten had subsequently required surgery and 97 remained untreated.

In the majority, symptoms did not worsen and only 2 developed acute retention. Urodynamic studies, where repeated, showed little change.

Although there was no certain indicator of progression, a flow rate measurement could identify the patients at risk of clinical deterioration sufficient to require surgery.

Troublesome lower urinary tract symptoms are a common cause of referral to a urological clinic. The symptom-complex of frequency, urgency, nocturia, hesitancy and a poor stream in a middle-aged or elderly man has conventionally been called "prostatism", but this is a misleading term since it implies the existence of a prostatic obstruction which may not be present (Turner-Warwick, 1979). Both patient and surgeon are anxious to know whether the symptoms are likely to be progressive and whether there is a risk of acute retention. The surgeon would prefer to perform an elective operation (Blandy, 1978).

Between 1974 and 1976 318 patients with symptoms suggesting bladder outflow obstruction were assessed by routine clinical, radiological and urodynamic investigations. Pressure-flow studies showed that 67% had obstructed micturition (Abrams and Feneley, 1978): 107 of the patients from this series who, on clinical grounds, did not undergo elective surgery at that time have been reviewed 5 years later; 53 of these had initially been considered to be obstructed on urodynamic testing.

Patients and Methods

One hundred and seven patients were reviewed, mean age 61.9 years (range 45-80) when first assessed.

Ten had required surgery in the interim.

Sixty-four returned for reassessment; their symptoms were recorded on the same standard proforma and a urinary flow rate was obtained: 43 of these agreed to have their urodynamic studies repeated, consisting of filling and voiding cystometry (Abrams and Feneley, 1978) and a urethral pressure profile study (Abrams, 1976), conducted by the same techniques and under similar conditions as previously. The mean review period was 65 months (range 55-73 months).

The remaining 33 patients answered a postal symptom-questionnaire.

On the original urodynamic tests the criterion used in the diagnosis of outflow obstruction was a urethral resistance factor (P_{ves}/Q^2)>0.5.

The statistical methods employed were the Student's "t" test, paired "t" test, Wilcoxon's rank sum test, and correlation coefficient (r) analysis. Two-tailed statistical significance was judged at the 5% level.

Results

Symptoms

Of the 97 patients who did not have surgery, 16 considered their condition to have deteriorated. On detailed questioning 19 admitted to worsening of their hesitancy or poor stream, symptoms previously associated with outflow obstruction on pressure-flow studies (Abrams and Feneley, 1978): 15 reported an increase in their "irritative" symptoms of frequency, urgency or nocturia. The majority were unchanged or slightly better (Table 1).

Urinary Peak Flow Rates

Measurements were repeated in 64 patients (mean age when first seen 60.6 years). Thirty-one of

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 1 Symptomatic Changes Over 5 Years (97 Patients)

	Overall	*Obstructive symptoms*	*Irritative symptoms*
Worse	16	19	15
Better	31	16	24
Same	50	62	58

these had been considered obstructed on their original urodynamic assessment. To allow for variation in flow rate due to different voided volumes the values were interpreted by means of the nomogram described by Siroky *et al.* (1979), whereby for a given bladder volume a peak flow rate is expressed in terms of standard deviations (SD) from the normal. Thirty-nine fell, 16 rose and 9 were exactly the same; the fall in the group as a whole was significant (Table 2).

Allowing for variation in flow rate in the same individual, a change of at least 1.2 SD on the nomogram is required to signify a probable change in outflow resistance (Siroky *et al.*, 1979); 6 patients exhibited a fall by this amount, only 3 of whom actually complained of a worsening stream.

Flow rates decrease with advancing age (von Garrelts, 1957); a linear approximation of the rate of fall is 2.1 ml/s per 10 years in the normal population (Drach *et al.,* 1979). Extrapolating that figure to this series the observed fall of 1.2 ml/s (Table 2) does not differ significantly from the 1.1 ml/s which could be expected due to ageing.

Moreover, it has been shown that the fall in flow rate with age is less pronounced in patients with outflow obstruction (Drach *et al.*, 1979). In this series the average fall in patients with flow rates lower than −2 SD, a level which has 98% correlation with clinical evidence of outflow obstruction (Siroky *et al.*, 1980), was only 0.08 nomogram units, compared with 0.49 in the remainder. The latter still does not significantly differ from Drach's figures for the normal population.

Table 2 Changes in Urinary Peak Flow Rate (64 Patients)

	Flow rate (ml/s)	*Flow rate (SD)*
1975	13.1	−1.97
1980	11.9 ($P<0.02$)	−2.23 ($P<0.01$)

Table 3 Changes in Urodynamic Data (43 Patients)

	Up	*Down*	*Same*	*Overall*
Residual urine	16	15	12	Down by 16 ml ($P>0.1$)
Bladder capacity	16	12	15	Up to 2 ml
Voiding detrusor pressure	15	21	6	Down by 4 cm H_2O ($P>0.1$)

Urodynamic Studies

Changes in urodynamic data are given in Table 3 and Figures 1 to 3. Alterations empirically recorded as a change were 20 ml for residual urine, 50 ml for cystometric capacity, and 5 cm H_2O for voiding detrusor pressure. Seventeen of the 43 patients retested had initially been considered obstructed.

Residual Urine (Fig. 1)

Eight of the 16 patients with increased residual urine had none on the original tests, but the largest to develop from zero was 60 ml. The largest recorded was 340 ml in a patient who had a residual of 450 ml in 1975 associated with a low voiding pressure of 20 cm H_2O which remained unaltered.

Bladder Capacity (Fig. 2)

Although there was no change in the group as a whole, 8 of the 12 patients whose cystometric capacity fell did complain of worsening irritative symptoms.

Voiding Pressure (Fig. 3)

Intrinsic detrusor pressures (P_{ves}-P_{abd}) at maxi-

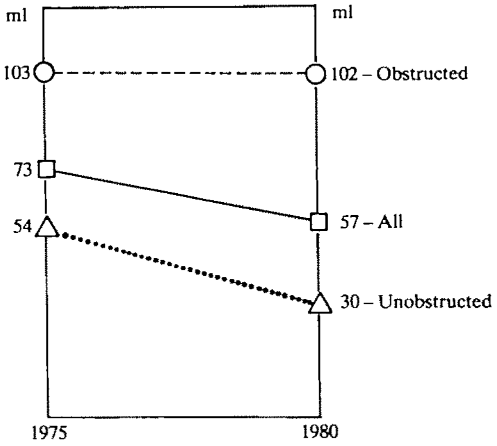

Fig. 1 Residual urine (mean values on initial and subsequent testing in 43 patients)

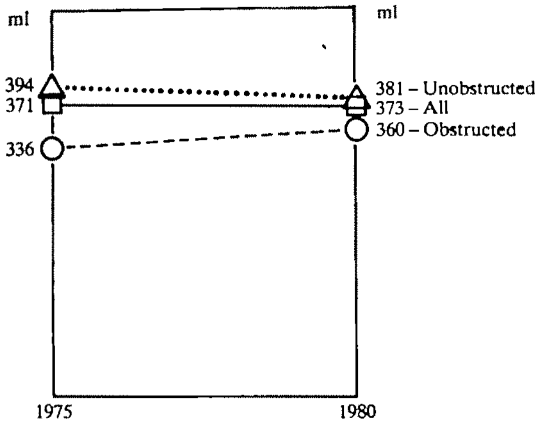

Fig. 2 Bladder capacity at cystometry (mean values on initial and subsequent testing in 43 patients).

mum flow are quoted; one patient was excluded for technical reasons. Voiding pressure fell more often than it rose, but any change was independent of the value recorded 5 years previously. Where it did fall, there was a weak correlation with an increase in residual urine ($r=0.40$; $0.1 > P > 0.05$).

Detrusor Instability

Of the 97 patients reviewed symptomatically, an unstable bladder had been demonstrated in 49 on original testing. Only 3 of these felt their irritative symptoms were worse. Seventeen patients retested had previously been shown to be unstable and 14 remained so (82%). One patient developed a minor degree of instability though remaining unobstructed. No patient deemed to have concomitant obstruction displayed a greater degree of instability 5 years on, 9 such patients being retested.

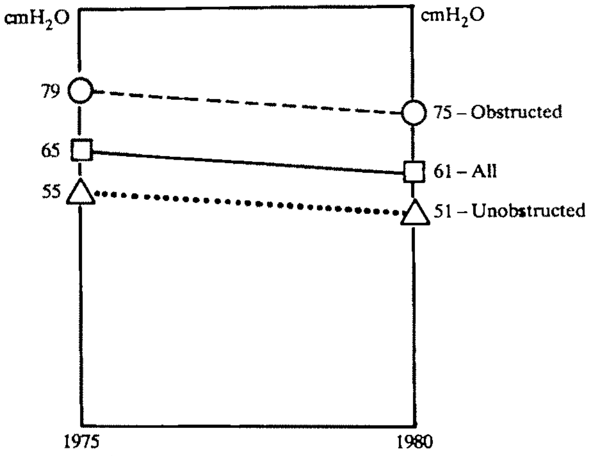

Fig. 3 Intrinsic voiding pressure (P_{ves}-P_{abd}) (mean values on initial and subsequent testing in 43 patients).

Urethral Pressure Profiles

No significant changes occurred. The prostatic pressure area, the derived expression which most closely correlates with urethral resistance (Abrams, 1976), rose very slightly from a mean of 88.7 units to 93.3 ($P>0.1$).

Prognostic Factors

In the patients re-assessed, no association with subsequent deterioration could be demonstrated with the original values for any of the parameters described, including urethral resistance factor, nor with urographic evidence of outflow obstruction (reported by a radiologist).

Patients Needing Surgery

The original findings in the 10 patients who did eventually require surgery, after intervals of between 18 months and 4 years, are shown in Table 4. Two developed acute retention; the other 8 complained of worsening symptoms, equally divided between the obstructive and irritative variety. On average, this group had significantly lower flow rates than the remaining 97 patients ($P>0.001$) and increased prostatic length on profilometry ($P>0.001$). In nomogram values, all had peak flow rates lower than 2 SD below normal; 8 were lower than −2.5 SD and 5 (including the 2 who developed retention) were lower than −3 SD. All had been classified as obstructed on urodynamic investigation and all had a prostatic length in excess of 5.5 cm. Detrusor instability had been demonstrated in 6.

Discussion

Symptoms are notoriously unreliable in the assessment of bladder outflow obstruction (Castro *et al.*, 1969). They have been shown to fluctuate with time in retrospective and prospective reviews (Clarke, 1937; Craigen *et al.*, 1969) and in drug trials involving a placebo (Castro *et al.*, 1971;

Table 4 Mean Values in 10 Patients Who Required Subsequent Surgery (Values for 97 Untreated Patients in Brackets)

Peak flow	8.1 ml/s	(13.2)
	−2.86 SD	(−1.97)
Residual urine	76 ml	(55)
Bladder capacity	295 ml	(335)
Detrusor pressure	88 cm H_2O	(73)
Prostatic length	6.7 cm	(5.1)

Abrams, 1977). In this series only a minority worsened symptomatically over a 5-year period and the incidence of acute retention was very low (1.9%).

Although prostatic size correlates poorly with the degree of outflow obstruction it produces (Turner-Warwick *et al.*, 1973), it is interesting that all of the patients who later required surgery had large glands.

The urodynamic results altered little over 5 years and none was shown to be an accurate indicator of progressive obstruction. All patients whose clinical deterioration had led to surgery were considered obstructed on pressure-flow studies, but no precise definition of obstruction exists. Half of the patients in this series had originally been classified as obstructed, so that the criterion used then may not seem valid with hindsight. Indeed, the very concept of combining pressure and flow measurements into a "urethral resistance factor" has been criticised (International Continence Society, 1980).

In retrospect, the simplest and least invasive test, the urinary flow rate, was as good a screening procedure as any other. No patient with a peak flow rate within 2 SD of normal required surgery during the review period (equivalent to 13 ml/s at bladder volume of 250 ml). However, to attempt to define indications for prostatectomy it is necessary to draw comparison, over a similar period, with patients who did have operative treatment. A study to this end is now in progress.

Acknowledgements

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A Comparison Between Digital Examination and Per-rectal Ultrasound in the Evaluation of the Prostate

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Summary—Three hundred and fifty-two patients have been examined by per-rectal ultrasound and histological confirmation of the diagnosis was obtained in 242 cases. Per-rectal ultrasound compared favourably with digital palpation both as a method of diagnosing prostatic cancer and also as a method of staging a primary tumour. Confirmation of the accuracy of this technique as a method of staging was gained by a study involving the use of cadaver material.

Repeat examinations on patients with prostatic carcinoma have shown that per-rectal ultrasound is an ideal method for monitoring response of the primary tumour to treatment.

It is now 7 years since Watanabe *et al.* (1974) published their description of the development and application of new equipment for transrectal ultrasonography. In this short time, technological progress has been such that the relatively simple bistable scans obtained by Watanabe, which were capable of defining capsular echoes but little in the way of internal structure, have been superseded by grey scaled images, which allow detailed examination of the gland parenchyma. Additional developments, such as the measurement of gland volume with the aid of an electronic cursor, suggest that the age of the computer has now arrived and prompt the question—is our index finger now redundant?

In cancer of the prostate, digital palpation is performed to make the initial clinical diagnosis, to stage the primary tumour and subsequently to judge the response of that tumour to treatment. If the finger was to be superseded as a diagnostic tool, ultrasound must prove itself superior in all 3 respects. One would also hope that it would be able to detect subclinical cancer, where the diagnosis had been missed on digital palpation. This paper reports our experience with per-rectal ultrasound both in the diagnosis and staging of primary prostatic cancer.

Patients and Methods

Three hundred and fifty-two patients have been examined using per-rectal ultrasound. Seventy-six of these patients were examined on 2 or more occasions. In the whole series there were 7 examination failures, mostly because of local discomfort. Two patients experienced hypotensive episodes during examination, both of which proved transient. Over 3 years there has been only one examination refusal.

All of the scans were performed using the Aloka chair mounted per-rectal probe. This incorporates a concave transducer of 1.0 cm diameter and 3.5 MHz frequency, which rotates about a vertical axis scanning the perpendicular plane. The probe was coupled to a Searle Pho-Sonic "B" Scanner, photographing the scans produced with a Birchover Multiformat Camera Back.

Prior to scanning, all patients in the clinical services were submitted to digital examination by either P.J.C.B. or W.B.P., and in most cases by both. A record of clinical findings was kept for later comparison with the ultrasonic and histological results.

All scans were independently assessed by G.J.G., who had no knowledge of the diagnosis or symptomatology.

Diagnostic Criteria

Over the last 3 years we have gradually evolved a set of criteria for the ultrasonic diagnosis of prostatic disease. Figure 1 illustrates the appearance of a normal prostate. The capsule is seen clearly and appears well defined. It has a typical crescentic shape. The internal structure is homo-

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Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

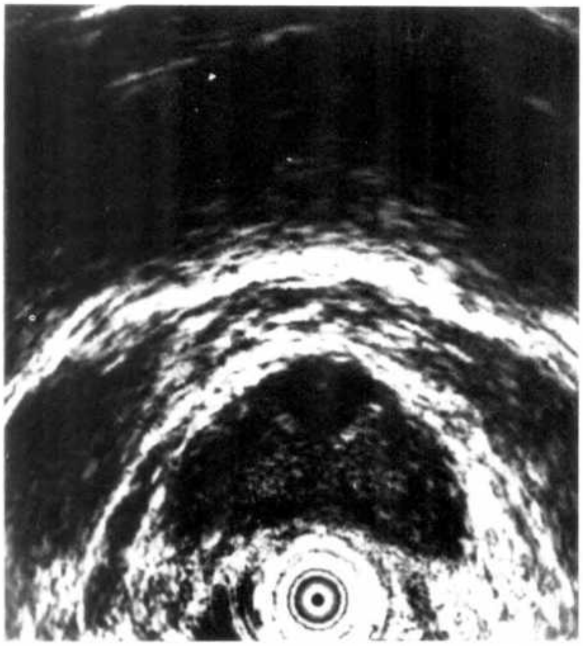

Fig. 1 Normal prostate.

geneous apart from a circular anterior sonolucent area, which probably represents the periurethral glands so often demonstrated in the younger subjects.

Scanning at a higher level, the bladder base and seminal vesicles can be seen (Fig. 2). Since it is possible to scan to a maximum depth of 10 cm only, it is not always possible to see these structures, particularly in obese subjects with large hyperplastic glands. Figure 3 shows a typical example of benign prostatic hyperplasia where the internal structure is fairly homogeneous and the capsule is well defined but now adopts a globular shape. The larger nodules appear to be demarcated by thin transonic lines. Figure 4 illustrates the appearance of a confined carcinoma of the prostate. The capsule is well defined and appears to be intact. The parenchymal echo pattern is not homogeneous but shows abnormal middle range echoes in the right lobe. These are typical of 2 conditions—confined carcinoma of the prostate, as in this case, and chronic inflammatory disease. Unfortunately, it is not yet possible to distinguish between these 2 conditions ultrasonically and such appearances are therefore labelled as consistent with either diagnosis, with a recommendation for biopsy. Figure 5 shows the appearance of an advanced unconfined cancer of the prostate. The prostatic capsule is grossly distorted, with evidence of discontinuity on the right anterolateral aspect.

To obtain confirmation of the reality of perrectal ultrasound as a method of staging prostatic cancer, 35 cadaver specimens were studied. The specimens consisted of bladder, prostate and rectum removed *en bloc* from cadavers. These were mounted in a special tank which contained a hole in its base over which the anus was fastened and

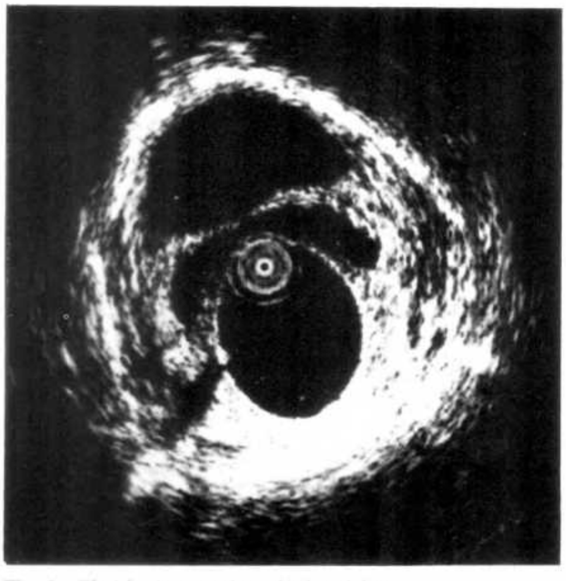

Fig. 2 Bladder base and seminal vesicles.

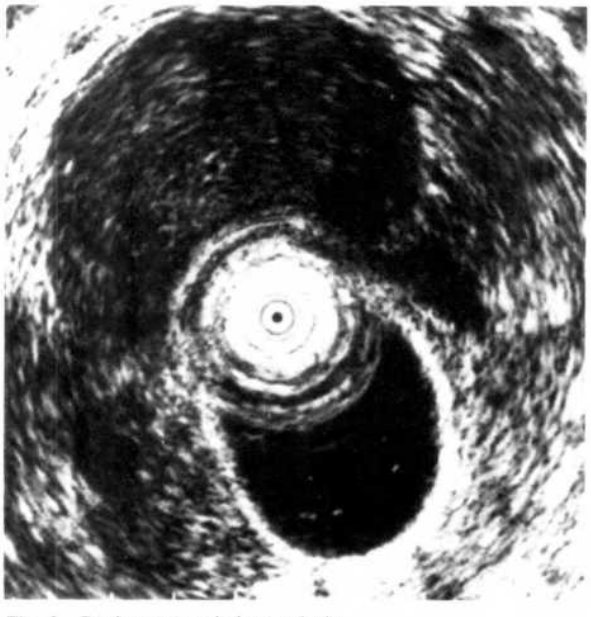

Fig. 3 Benign prostatic hyperplasia.

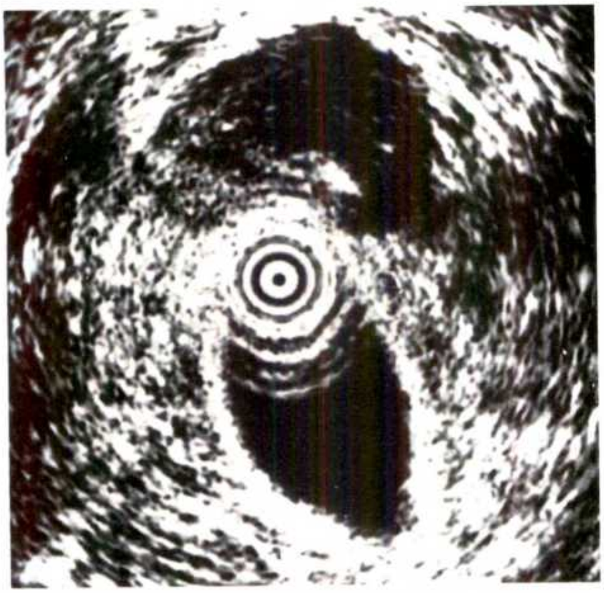

Fig. 4 Confined cancer of prostate (digitally T2).

through which the ultrasonic probe could be advanced into the rectum. After scanning, the prostates were sectioned in ½ cm steps along a plane comparable with that scanned by the transducer and histological sections were prepared for microscopic examination. In the cadaver series 6 specimens were found to have histological evidence of prostatic cancer with evidence of tumour extension beyond the capsule in 3. All 6 cases were correctly diagnosed as prostatic cancer by per-rectal ultrasound and all 6 cases were correctly staged using this technique. It is therefore evident that per-rectal ultrasound in these cases presented an accurate representation of the histopathological stage.

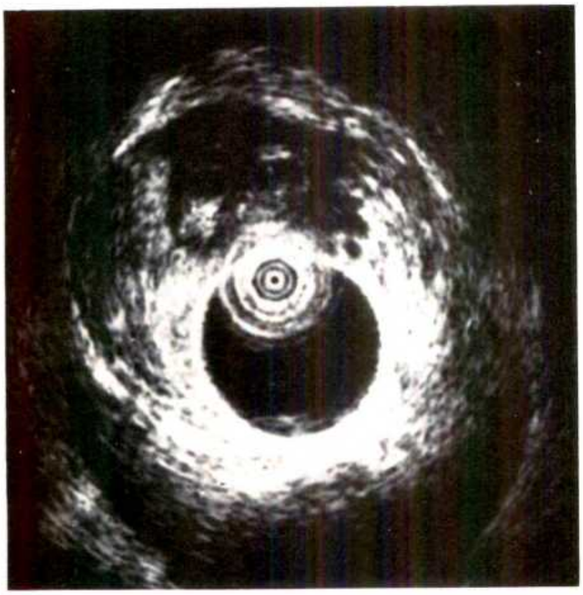

Fig. 5 Unconfined cancer of prostate (digitally T3).

Results

Of the 352 patients scanned, histological confirmation of the diagnosis was obtained in 242. Of these, 99 cases had evidence of prostatic cancer. On digital examination, 86 of these had been correctly diagnosed as malignant prostates, whereas ultrasonically, 91 cases were so diagnosed.

However, a further 87 cases were wrongly diagnosed as cancer on digital examination compared with 30 patients so labelled on ultrasonic examination, representing false positive diagnostic rates of 51 and 32% respectively.

Of the 13 cases of subclinical cancer, where the patient had a clinically benign gland with histological evidence of cancer, 11 were correctly diagnosed ultrasonically. In the whole series there were 8 cases of prostatic cancer which were missed at ultrasonic examination.

When staging of the primary tumour was considered, 46 of those patients with histologically proven carcinoma were staged as tumours still within the capsule and 40 were staged as clinically unconfined growths on digital palpation (Table).

Of the 46 clinically confined cases, ultrasonic examination revealed that 18 had evidence of discontinuity in the capsule and therefore it is likely that approximately 40% of the clinically confined tumours had been digitally understaged. In these cases the capsular breech was more often seen in the anterolateral aspect of the gland. Of the 40 patients with clinically unconfined cancer, in 33 there was capsular discontinuity ultrasonically.

In this group the capsular breech was evident more posteriorly, where it could be expected to be easily palpated by the examining finger.

Table Staging of Patients with Proven Prostatic Cancer

Digital diagnosis		*Ultrasonic diagnosis*	
		Confined	*Unconfined*
Confined	46	24	18
Unconfined	40	5	33

Discussion

These results indicate that per-rectal ultrasound was more efficient at diagnosing prostatic carcinoma than digital palpation. This was particularly evident in cases of subclinical disease, where 90% were diagnosed using per-rectal ultrasound.

We would suggest that this technique is a superior method of staging the primary tumour, mostly because of its ability to image the entire prostatic capsule. It is therefore capable of showing discontinuity of the anterolateral part of the capsule which may not be readily palpable *per rectum.* Per-rectal ultrasound was found to be of value in the follow-up assessment of patients with proven prostatic cancer. In several instances tumour progression was demonstrated ultrasonically several months before it became evident on digital palpation. There is no other way of providing objective data about a primary tumour which is so easily recordable and which is therefore available for comparison at later examinations to monitor response to treatment. Per-rectal ultrasound is able to diagnose prostatic cancer more efficiently than the index finger, particularly in cases of subclinical disease. It is superior as a method of staging the primary tumour and is an ideal method for the follow-up of patients in order to monitor their treatment response. At the present time diagnostic confusion arises in 2 main areas. One is the confusion between confined carcinomas and chronic inflammatory disease, and the other is difficulty in visualising the capsule at the apex of the gland, which sometimes leads to the mistaken diagnosis of unconfined cancer. However, we have litle doubt that with the development of less expensive or easily portable equipment, this method of examination will become generally accepted as the single most important method of evaluating the prostate.

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Prostatodynia—Physiological Characteristics and Rational Management with Muscle Relaxants

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Summary—Patients with a clinical diagnosis of prostatodynia were evaluated by bacteriological, urodynamic and psychological means. In a prospective study 27 patients were entered on a trial of phenoxybenzamine, baclofen and placebo. A 50% symptomatic response was reported with phenoxybenzamine.

The clinical diagnosis of prostatitis has been subdivided by analysis of the expressed prostatic secretion (EPS) into acute and chronic bacterial prostatitis, abacterial prostatitis and prostatodynia (Drach *et al.*, 1978).

Prostatodynia is widely recognised as being refractory to treatment which in the past has included prolonged antibiotic regimes and endoscopic resection of the prostate.

A study was therefore initiated to define the clinical, bacteriological, urodynamic and psychological characteristics of this disorder and from these results a treatment regime with muscle relaxants was undertaken.

Patients and Methods

Thirty-seven patients entered the study (mean age 42, range 21-69 years). The median length of history was 3 years (range 8 months to 10 years). The symptoms were perineal pain (76%), pain after ejaculation (56%), suprapubic discomfort (55%), penile pain (44%), testicular pain (35%) and loin pain (17%). Contrary to expectation, voiding complaints did not predominate, the commonest being terminal dribbling (35%), hesitancy (26%) and sensory urgency (23%). Only 17% felt that they had to strain to void. Most patients complained of frequency of micturition but objective assessment by frequency volume charts in their normal environment demonstrated significant changes in only 7 patients. Routine blood screen, intravenous urography and cystoscopy were essentially normal in all patients, apart from one who had diffuse induration of the prostate and enlargement of seminal vesicles. All patients had previously undergone prolonged courses of various antibiotics to no effect.

An attempt was made to obtain expressed prostatic secretion (EPS) in all patients, though in only 25 were adequate samples obtained. In 19 patients the pH of the EPS was less than 7, cell-free (<5 wbc per high power field) and sterile on culture. Two of the 6 patients with a pH greater than 7 had previously proven bacterial prostatitis but all were sterile and cell-free on entry to the trial.

Urine cultures (VB1—initial stream, VB2—midstream and VB3—post-massage urine) were sterile in all patients.

Urodynamic Evaluation

The mean urine flow rate in these patients was 16.2 ml/s±0.9 SE (Fig.). One patient was unable to void on any occasion. All patients had repeat urine flow measurements at subsequent visits to the clinic and for individual patients the mean urine flow rate rose with the second and third visit to give a mean of 19 ml/s, although the paired increases were not statistically significant. Urethral closure pressures were measured with the Brown and Wickham technique. The mean value of maximal urethral closure pressure (MUCP) was 121 cm water±9.23 SE. Cystometry was attempted in all patients, though catheterisation was possible in only 22 cases. All patients were stable with a mean capacity of 320 ml. Voiding studies demonstrated a mean intrinsic detrusor pressure of 34 cm water±2.2 SE associated with a mean flow rate of 15.0 ml/s±1.0 SE.

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

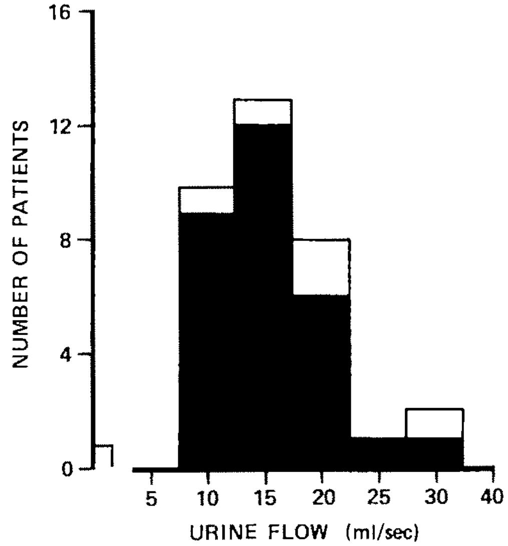

Fig. Peak urine flow rate in 35 patients with prostatodynia. Previous TUR of prostate ☐.

Psychological Evaluation

A psychological comparison of 14 patients of this study with anxiety state patients and a group of normal volunteers was made. The tests used were personality questionnaire, frontalis muscle EMG and heart rate changes during resting and stressful (mental arithmetic) conditions. Anxiety related symptoms, resting frontalis EMG and heart rate were statistically significantly higher in the patients of this study than in normal controls, but not significantly different from those found in anxiety patients. The urethral pressure profile measurements were found to correlate significantly with heart rate recovery in prostatodynia patients following mental arithmetic tests ($r = 0.52$ $P = <0.05$).

Drug Trial

Following clinical, bacteriological and urodynamic screening, patients underwent a double blind trial of phenoxybenzamine (alpha-adrenergic blocker) baclofen (striated muscle relaxant) and placebo. Treatments were given in random order and were each given for one month.

After each treatment the patient was reassessed, urine flow rates recorded and symptomatic response, if any, recorded. Repeat cystometric assessment was not made. At the end of the 3 months' course the patient was again asked which treatment he found the most beneficial, with the clinician being unaware of the treatment order. The dose of phenoxybenzamine was 10 mg *nocte* for 3 days and then 10 mg bd for one month. The dose of baclofen was 5 mg 3 times a day for 3 days and then 10 mg 3 times a day for one month. The placebo was lactulose capsules.

Results

Twenty-seven patients have completed the trial to date. Phenoxybenzamine produced a satisfactory symptomatic response in 13 patients, baclofen in 10 patients and placebo in 4 patients. In 7 cases no response was noted. Four patients had a symptomatic response to both phenoxybenzamine and baclofen. Two patients responded to both phenoxybenzamine and placebo and one patient responded to both baclofen and placebo. Only one patient responded to placebo alone. Using the McNemar test for analysis of treatment results, for phenoxybenzamine against placebo $P = 0.027$ and for baclofen compared to placebo $P = 0.09$.

Discussion

In this group of patients the symptoms and long duration of history are typical of prostatodynia. The diagnosis of prostatodynia, however, can only be made by analysis of the EPS, although it must be admitted that in patients who have had endoscopic prostatic resection, EPS may be unobtainable. For these patients bacterial infection has to be excluded by the examination of the urine voided after prostatic massage. The EPS in the present series of patients was cell-free and sterile at entry into the drug trial. The raised pH (>7) of EPS in 6 patients probably reflected previous bacterial infection as the pH of the prostatic secretion may take many months to return to normal after overt infection (White, 1975).

The urodynamic findings from this series of patients with prostatodynia have some similarity with those from men with the "anxious bladder syndrome" (George and Slade, 1979). Both groups have markedly raised urethral pressure profiles, stable bladders and low pressure—low flow voiding. The symptoms between the 2 groups are, however, different, for prostatodynia patients complain primarily of pain, whereas anxious bladder patients complain more of severe sensory frequency and voiding abnormalities.

The psychological tests performed in 14 patients in this series showed significantly increased anxiety levels and so contradicted the findings of Smart and Jenkins (1973). Our patients had long-standing symptoms but had had multiple previous investigations and various treatments without success. It might be considered, therefore, that these problems led to the underlying anxiety neurosis.

Since the EPS is sterile in patients with prostatodynia there can be no justification for prolonged courses of antibiotics. The urodynamic finding of an increased urethral pressure profile is consistent with increase in tone of the pelvic floor, and the increased mean EMG voltage of the frontalis muscle supports a generalised increased striated muscle tone. Treatment of prostatodynia with baclofen (a striated muscle relaxant) and phenoxybenzamine (an alpha-adrenergic blocker) is thus a logical step. Both drugs have been shown to reduce the urethral pressure profile (Donker *et al.*, 1972; Florante *et al.*, 1980), but we were able to repeat the UPP in only 2 patients, as the remainder were unwilling to undergo further urodynamic evaluation. In these 2 patients however we confirmed a fall of UPP after phenoxybenzamine.

The symptomatic response after phenoxybenzamine was 50% and after baclofen 37%. In contrast, the response to placebo was 8%. The response to phenoxybenzamine and baclofen was equally distributed between the 3 months of treatment and so the drug response did not reflect an order effect which is so important in cross-over trials. The *P* values for phenoxybenzamine and baclofen are 0.027 and 0.09 respectively. The accepted *P* value for clinical significance is 0.05 or less. The present trial is, however, complicated in that 3 drug treatments were used and the *P* value for statistical significance should be $0.05/3 = 0.019$; by this criterion the results for phenoxybenzamine, although clinically impressive, are not statistically significant.

To assess objective response we measured urine flow rate at the end of each treatment and recorded urine voiding frequency by frequency volume charts. Both tests demonstrated an improvement through the trial period which was irrespective of treatment. The commonest side effect with phenoxybenzamine was reflux ejaculation but 3 patients complained of lethargy and of feeling unwell and stopped the medication. Despite reflux ejaculation, several patients at their own request remained on phenoxybenzamine after the drug trial because of the symptomatic relief.

We did not resect the prostate in any of our patients with chronic prostatitis since this affects the peripheral rather than the central zone of the prostate, and therefore TUR theoretically is unlikely to be of benefit (Blacklock, 1980). In support of this is the report of Smart *et al.* (1976) that an initial response of TUR of prostate for prostatitis was not maintained.

In conclusion, we would suggest that the syndrome of prostatodynia has fairly consistent symptoms and urodynamic abnormalities and is associated with an increased level of anxiety as measured by psychological tests. Treatment with muscle relaxant drugs such as phenoxybenzamine and baclofen has been shown to be of great benefit to many of the patients in this study.

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Cardiovascular Complications in the Treatment of Prostatic Carcinoma

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Summary—Cardiovascular complications in patients with carcinoma of the prostate have been studied in relation to 3 methods of treatment, namely stilboestrol, estramustine phosphate (Estracyt) and bilateral orchiectomy. One hundred and sixteen patients were studied over a 4-year period on a prospective basis, 48 being treated with stilboestrol, 31 with estramustine and 37 with bilateral orchiectomy. The incidence of the cardiovascular side effects of these 3 treatment regimes in the first year of treatment was recorded after the patients had been divided into those with localised (M0) disease and advanced disease with metastases (M1).

In patients treated with stilboestrol 29% had cardiovascular complications with a mortality rate of 16%. With estramustine 25% had complications with a 16% mortality rate, but with orchiectomy the complication rate was only 8% with a 3% mortality rate. It is recommended that stilboestrol and estramustine phosphate should not be used in the presence of cardiovascular disease and that the primary form of treatment in prostatic carcinoma should be bilateral orchiectomy, especially in patients with localised disease.

Since the work of Huggins and Hodges (1941), stilboestrol and bilateral orchiectomy have been widely used in the routine management of carcinoma of the prostate. Oestrogen therapy is, however, associated with an increased risk of cardiovascular complications (Byar, 1973; Blackard, 1975; Abbou, 1980). Bracci (1979) abandoned the use of oestrogens in favour of anti-androgens because of these alleged cardiovascular complications. The purpose of this study was to find out whether hormone therapy does increase the risk of cardiovascular side effects.

Patients and Methods

One hundred and thirty-eight patients with histologically proven carcinoma of the prostate were available for study over a 4-year period but of these only 116 could be analysed in any detail: 48 were treated with stilboestrol 1 mg tds, 31 with estramustine phosphate (Estracyt) 280 mg bd for 2 months, reducing to 140 mg bd thereafter, and 37 had a bilateral orchiectomy (total or subcapsular) as their primary form of therapy. All those who received stilboestrol or estramustine phosphate had been studied prospectively as they were treated according to the EORTC Trial, Protocol No. 30762. Most of the patients having bilateral orchiectomy were also studied prospectively but in a few the details were obtained from a retrospective evaluation of the hospital notes. In some cases it proved difficult, particularly in the retrospective part of the study, to determine the cardiovascular status of the patients before they started treatment. The incidence of cardiovascular complications was noted with particular reference to deep venous thrombosis, pulmonary embolus, myocardial infarction, cerebrovascular accidents, congestive cardiac failure and severe oedema.

Patients in this series have been followed up for at least one year after the start of treatment and they have been treated with only stilboestrol, estracyt or bilateral orchiectomy. All 116 men, average age 72 years, had histologically proven carcinoma of the prostate and in addition to noting any cardiovascular complications, all patients had bone scans before starting treatment and X-rays of any "hot spots", to see if the disease was confined to the prostate gland (M0) or whether there was evidence of metastases (M1) (UICC, 1978). Table 1 shows the distribution of the 116 patients between localised and metastatic disease by treatment and from this it can be seen that 54% of the patients had localised

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Table 1 Primary Treatment of Prostatic Carcinoma

	M0	*M1*	*Total*
Stilboestrol	29	19	48
Estramustine	19	12	31
Orchiectomy	15	22	37
Total	63 (54%)	53 (46%)	116

disease and 46% evidence of metastases at the initial diagnosis. The number of patients who died from progression of their prostatic cancer within a year of treatment was 19 out of 116 (16%), the distribution being given in Table 2. This table shows that in localised disease there were no deaths out of 29 patients treated with stilboestrol, one death out of 19 patients treated with estramustine and one death with bilateral orchiectomy, giving a total of only 2 deaths due to cancer out of 63 patients with localised disease. As one would expect in the advanced metastatic disease group 6 died out of 19 who were treated with stilboestrol, 5 out of 12 with estramustine and 6 out of 22 who had bilateral orchiectomy, giving a total of 17 out of 53 patients with metastatic disease. Overall, 19 out of 116 died from their prostatic carcinoma in the first year of treatment, the deaths being reasonably well distributed between each of the 3 treatment arms.

One of us (R.W.G.), particularly in the latter part of the investigation, tended to perform bilateral orchiectomy as a primary treatment, particularly on patients with a previous history of cardiovascular problems, and therefore the selection of patients has been slightly biased, but consideration of the complications has shown this action to be justified.

Results

Each patient was reviewed on a regular basis, information regarding any history of a deep venous thrombosis, pulmonary embolus, myocardial infarction, cerebrovascular accident, clinical evidence of congestive cardiac failure and the presence or absence of severe oedema being recorded on each visit. Minor degrees of oedema were ignored. Where death occurred all possible enquiries were made to establish the exact cause of death and it is interesting to note that 3 patients, who had been diagnosed on clinical grounds as having died of myocardial infarction, had at post mortem a fatal pulmonary embolus almost certainly originating in the deep veins of the pelvis, which can be difficult to diagnose clinically.

Table 2 Deaths Due to Carcinoma in Relation to Treatment Received

Treatment	*Number in group*	*Death due to carcinoma*		*Total*
		M0	*M1*	
Stilboestrol	48	0/29	6/19	6/48
Estramustine	31	1/19	5/12	6/31
Orchiectomy	37	1/15	6/22	7/37
Total	116	2/63	17/53	19/116

Table 3 shows the cardiovascular complications following stilboestrol therapy. Fourteen of 48 patients had some form of complication, mainly in the localised disease group. Of 29 patients with localised disease 4 had pulmonary embolus and 3 died, 4 had myocardial infarcts and 2 died, one had a cerebrovascular accident which proved fatal and 3 had congestive heart failure from which one died, giving a complication rate in this group of 12 out of 29 with 7 deaths. In the metastatic group there were only 2 complications out of 19, both fatal, one due to a pulmonary embolus and the other to a myocardial infarct. Therefore, of the 48 patients treated with stilboestrol 14 (29%) showed evidence of cardiovascular complications and 9 died, giving a mortality rate of 16%. It is disturbing to note that 12 of the 14 complications and 7 of the 9 deaths occurred in the localised disease group, in which there were no deaths due to carcinoma.

Table 3 Complications of Stilboestrol

	M0		*M1*		*Total*
Number of patients at risk	29		19		48
Complications	*No.*	*Deaths*	*No.*	*Deaths*	
Venous thrombosis	—	—	—	—	—
Pulmonary embolism	4	3	1	1	5
Myocardial infarction	4	2	1	1	5
Cerebrovascular accident	1	1	—	—	1
Congestive heart failure	3	1	—	—	3
Severe oedema	—	—	—	—	—
Total	12	7	2	2	14 (29%)

Number of deaths—9 (16%).

The complications of estramustine phosphate are shown in Table 4. Of 31 patients 19 had localised disease and of these 5 had cardiovascular complications, 2 of which proved fatal. Two patients had deep venous thrombosis, one of whom died; one had a myocardial infarction and died; one had a cerebrovascular accident from which he recovered and one patient had severe oedema which presented within 6 weeks of starting treatment and which settled only after the treatment was discontinued and the patient had a bilateral orchiectomy. In the advanced group there were 3 patients with complications, all of which proved fatal: these were a myocardial infarction, a cerebrovascular accident and severe congestive cardiac failure. Thus out of a total of 31 patients, 8 (25%) developed cardiovascular complications and 5 of them died (16%); when compared with the stilboestrol group the complications were much more evenly distributed between localised and metastatic disease.

The complications following bilateral orchiectomy are summarised in Table 5 and are remarkably few in number. In the localised group only one patient developed severe oedema which proved to be non-fatal and in the advanced group 2 patients developed congestive cardiac failure, one of whom died, giving a total complication rate for the series of only 3 out of 37 (8%) with a mortality of only one out of 37 (3%), which compared very favourably with the other 2 forms of treatment.

When these results are combined and presented in Table 6 it can be seen that although the figures are not large there is a far higher incidence of cardiovascular complications with stilboestrol and estramustine phosphate, both carrying a mortality rate of 16%, where the mortality is due to cardiovascular complications of treatment and not the disease. With bilateral orchiectomy the cardiovascular complication is very much lower (8%) and the mortality rate only 3%. Statistically these figures quite clearly indicate that both stilboestrol and estramustine have a much higher rate of cardiovascular complications and an unacceptable mortality compared with orchiectomy. These patients, so far as can be determined, died not from prostatic cancer but from the complications of treatment and there would seem, therefore, to be little justification for using either drug, certainly with localised prostatic disease, if the side effects are going to cause more problems than the condition itself. It is reasonable to suppose, in any group of elderly men with an average age of 72, that there will be evidence of cardiovascular problems, yet the group who had bilateral orchiectomy, who were also of the same average age, did not appear to develop nearly so many complications. There would seem to be little doubt, therefore, that bilateral orchiectomy is a much safer treatment with fewer side effects. Bilateral orchiectomy can be performed quite easily even

Table 4 Complications of Estramustine Phosphate

	M0		*M1*		*Total*
Number of patients at risk	19		12		31
Complications	*No.*	*Deaths*	*No.*	*Deaths*	
Venous thrombosis	2	1	—	—	2
Pulmonary embolism	—	—	—	—	—
Myocardial infarction	1	1	1	1	2
Cerebrovascular accident	1	—	1	1	2
Congestive heart failure	—	—	1	1	1
Severe oedema	1	—	—	—	1
Total	5	2	3	3	8 (25%)

Number of deaths—5 (16%).

Table 5 Complications of Bilateral Orchiectomy

	M0		*M1*		*Total*
Number of patients at risk	15		22		37
Complications	*No.*	*Deaths*	*No.*	*Deaths*	
Venous thrombosis	—	—	—	—	—
Pulmonary embolism	—	—	—	—	—
Myocardial infarction	—	—	—	—	—
Cerebrovascular accident	—	—	—	—	—
Congestive heart failure	—	—	2	1	2
Severe oedema	1	—	—	—	1
Total	1	—	2	1	3 (8%)

Number of deaths—1 (3%).

Table 6 Complications and Deaths Expressed as Percentage

	Patients at risk	*Complications (%)*	*Deaths (%)*
Stilboestrol	48	29	16
Estramustine	31	25	16
Orchiectomy	37	8	3

in patients whose general condition is very poor and, if necessary, can be carried out quite successfully under local anaesthesia.

The analysis of this series certainly seems to support the findings of the VACURG Study (Blackard, 1975), although in that series a higher dose of stilboestrol was used. Jonsson *et al.* (1977) recorded 7 out of 154 advanced prostatic cancer patients with cardiovascular complications following the use of estramustine, but Mittelman *et al.* (1976) recorded no such side effects in 50 patients with Stage D disease. Hedlund (1979), who used 840 mg of estramustine per day in 106 patients, recorded an 18% incidence of thromboembolism, 17% ischaemic heart disease and a 34% incidence of congestive cardiac failure. He also noted that 50% of all complications occurred within 2 months of starting treatment. In our series the mortality rate for the complications showed that 7 out of 15 died within 3 months and 11 out of 15 died within 6 months of starting treatment.

Four patients who developed angina on stilboestrol therapy had their stilboestrol stopped and a bilateral orchiectomy performed. In all 4 cases the symptoms of angina ceased and the patient's general condition improved.

Statistically the χ-squared test for all complications, stilboestrol versus estramustine versus orchiectomy, gives a 9.3 value at 2 degrees of freedom (P 0.01-0.02). The test for deaths gives a value of 8.0 at 2 degrees of freedom (P 0.01-0.02). These both indicate a significant difference between the 3 treatment arms because of the lower rate of complication in the orchiectomy group.

This difference is not upheld when the M1 cases are examined alone. However, the difference between stilboestrol, estramustine and orchiectomy in the M0 cases are significant at less than the 5% level, when Fisher's exact test is applied.

Coagulation Study

A preliminary investigation to determine whether patients on oral oestrogens had an increased tendency to coagulation defect was performed in patients who underwent transurethral resection for both benign and malignant conditions of the prostate gland. Anti-thrombin factor III estimated by a chromogenic substrate method and serum fibrinogen levels was performed pre-operatively and on 5 other occasions in the post-operative period. Although there were variations in the results obtained there was no clear pattern and the investigation was discontinued.

The recommendations of this study are:

1. Stilboestrol in the dose of 1 mg 3 times a day or estramustine in the dose of 240 mg bd should not be used in localised prostatic cancer.
2. Stilboestrol or estramustine should not be used in patients with a previous history of cardiovascular disease.
3. Bilateral orchiectomy seems to have minimal cardiovascular side effects and should be considered the primary form of treatment in prostatic carcinoma, particularly in patients with localised disease.

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Half-body Irradiation in the Treatment of Metastatic Prostatic Carcinoma

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Summary—High dose radiation therapy given as a single fraction to the upper and lower halves of the body gives effective palliation for metastatic solid tumours. This treatment modality appears to be particularly effective in tumours which may have a slow doubling time such as carcinoma of the prostate.

Fifty-two patients with metastatic carcinoma of the prostate involving the skeletal system have received half-body irradiation. All had prior treatment with additive hormones or orchiectomy and the majority had received localised irradiation and/or chemotherapy. Significant immediate pain relief was achieved in 42 out of 52 patients (80%). This pain relief was maintained until death in 29 out of 43 patients (67%). Pain relief in responders appears to occur within 24 to 48 h of treatment.

A consideration of tumour cell kinetics suggests that therapy producing a 1 log cell kill may achieve a prolonged survival (Bergsagel, 1971). A whole body dose of about 1000 cGy could produce a 2 to 3 log cell kill. This appears to be true in plasma cell myeloma (Rowland, 1980). It has been shown that such large doses of radiation can be safely given by treatment of halves of the body, allowing a treatment gap of 4 to 6 weeks for marrow recovery (Fitzpatrick and Ryder, 1976).

In metastatic prostatic carcinoma bone is the dominant site of the disease in almost all cases, causing chronic, diffuse pain. Relief can often be produced by pituitary ablation, systemic radioactive phosphorous or localised irradiation. Although patients may benefit from chemotherapy, impressive responses are rare and the toxicity involved may not be acceptable at what is often a pre-terminal phase of the disease.

In a pilot study (Rowland, 1979) it appeared that half-body radiation therapy might be particularly beneficial when used to treat slow doubling time tumours such as prostatic carcinoma. In this report we give the results of this method of treatment in 52 patients suffering from metastatic prostatic carcinoma.

Patients and Methods

All patients had documented, widespread skeletal deposits evidenced by bone scan, radiographs and acid phosphatase measurements. All had escaped hormonal control and had often received marrow-compromising localised radiation or chemotherapy. Bone marrow examination in the first 15 patients before and after treatment showed involvement in all cases. This invasive investigation was not performed in later patients as the results did not influence our management.

Technique

All patients were treated with 8 MeV X-rays at a source skin distance of 200 cm to obtain the large fields required. A high dose rate of around 100 cGy/min was used. This meant that sick patients did not lie in the supine, prone or lateral decubitus treatment position for more than about 10 min.

The subcostal region was used to divide the fields, any field overlap in this region being acceptable and occurring where bulk soft tissue disease might be anticipated to be present.

The half of the body causing most symptoms was treated first, the other half being treated some 4 to 5 weeks later to allow for marrow recovery and assessment of response. A maximum tissue dose of 750 cGy to the upper half of the body (no lung correction) and 1000 cGy to the lower half of the body was given. No shielding was used but in the last 10 patients the parotid glands were kept out of the direct radiation beam by suitable positioning. Two patients had retreatment of previously irradiated areas, giving 4 half-body treatments in each case. If large metastases were present in weight-bearing bones such as the femur, further localised radiation was given.

A pre-treatment infusion of intravenous saline,

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potassium, steroids and anti-emetics was given over a period of 2 h before treatment. Large doses of steroids (up to 20 mg of dexamethazone) seemed particularly effective in controlling radiation sickness.

Pain relief was initially assessed by linear analysis but interpretation proved extremely difficult and it soon became obvious that if pain relief were to occur it would be immediate, striking and lead to rapidly improved mobility.

Results

Fifty-two patients were treated in this study, 44 having both halves of the body irradiated. Significant pain relief occurred within 48 h of treatment in 42 out of 52 patients (80%) and significantly was maintained until death in 29 out of 43 patients (67%). Thirty-eight of our patients died within the first 12 months of treatment. However, it is of interest that 3 patients were alive and pain free at 42, 30 and 30 months respectively.

Complications

Nausea and vomiting occurred in all patients, usually worse on upper half treatment, but seemed to be well tolerated and significantly eased by the pre-treatment infusion. All patients were warned that transient bowel symptoms might occur about 10 days after therapy, easily controlled by anti-diarrhoeal drugs. Xerostomia, a known complication of radiation therapy of the salivary glands, proved troublesome in some 40% of patients treated early in the study. However, recovery occurred by 6 months. Subsequently it proved possible to spare the parotid glands by suitable positioning of the patient. All patients having the upper half of the body treated developed alopecia but regrowth occurred by 4 to 6 months. Acute radiation pneumonitis was not observed in any of our cases.

Serial measurements of the peripheral blood counts showed that return to pre-treatment levels occurred within 4 to 6 weeks in the majority of cases. Some patients did, however, require regular transfusions to maintain the haemoglobin level, a point which should be specifically mentioned to the general practitioner since 2 of our patients who had responded well and whose only problem was anaemia were allowed to die as cases of terminal cancer, without transfusion. In 2 patients dying in hospital death was shown to be due to marrow failure.

Discussion

Half-body irradiation appears to be relatively well tolerated and may provide effective, prolonged symptomatic relief for patients suffering pain in the terminal stage of their disease. Many visits to hospital, which in our region may involve round trips of up to 125 miles, have been avoided for patients, friends and relatives and the benefits for patients and the Health Service are clear.

In all of our patients the bone marrow had been severely compromised by tumour involvement or previous therapy, but the fact that we have a few long-term survivors suggests that marrow failure is not inevitable. This is in keeping with our findings for other tumours such as breast and myeloma. Indeed, haematological tolerance for high dose single fractions may be higher than for multi-fraction irradiation (Loeffler, 1981). The last 10 patients treated have received Deca-durabolin 100 mg IM prior to therapy in the hope of maintaining marrow function. No adverse effects have been noted so far and in view of the hormone resistant status of these patients its routine use may prove beneficial and merits further attention.

We have observed no cases of fatal radiation pneumonitis and believe this is due to the use of high dose steroids, high energy X-rays and limitation of dose to the upper half of the body.

It is likely that the hormone-resistant phase of prostatic cancer is due to the growth of aggressive poorly differentiated clones of cells and it seems that the use of systemic radiation therapy at an earlier stage of the disease may provide survival benefit.

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Critical Evaluation of Direct Vision Urethrotomy by Urine Flow Measurement

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Summary—Fifty-two male patients were studied prospectively to assess the results of direct vision urethrotomy in the treatment of urethral strictures. The prognosis was found to be significantly worse in those patients who had received extensive previous treatment. A catheter is recommended for at least 3 days and for 4 weeks in patients who have had minimal previous treatment or who have impaired detrusor function. The use of a urine flowmeter is essential for determining the success of treatment and stricture recurrence. Measurement of the recurrence-free period is important for assessing progressive improvement following repeat urethrotomy and for determining which patients cannot be cured by direct vision urethrotomy.

Following Sachse's publication in 1974, direct vision urethrotomy has become increasingly popular as the primary procedure of choice in the management of most urethral strictures (Smith *et al.*, 1978; Gaches *et al.*, 1979, Johnston *et al.*, 1980). The advantages of direct vision urethrotomy have been fully expounded and include subjectively better results than with urethral bouginage, a very low recurrence rate and a remarkably low morbidity. However, the limitations of this method are still to be fully realised.

Patients and Methods

Fifty-two male patients were studied prospectively to assess the results of direct vision urethrotomy in the treatment of urethral strictures. The patients were aged 18 to 85 years with a uniform distribution and a mean age of 53: 47 patients presented with a poor stream, 2 with acute retention and 3 with a urethroperineal fistula. Direct trauma and previous urological surgery were the 2 most common causes of stricture formation (Table 1). The patients were classified into a low treatment group if they had had up to 5 previous operative procedures and a high treatment group if they had had more than 5 previous procedures: 28 were in the low treatment group, of whom 11 were first-time diagnoses, and 24 were in the high treatment group, having had between 6 and 192 previous procedures.

Table 1 Aetiology of Urethral Strictures

Trauma	16
Transurethral surgery	11
Open prostatectomy	3
Gonorrhoea	6
Non-gonococcal prostatitis	4
Idiopathic	12
Total	52

Pre-operative assessment of these patients included urine culture, intravenous urography, ascending urethrography and urine flow measurements. Direct vision urethrotomy was performed under general or sometimes local anaesthesia according to the technique originally described by Sachse (1974). Each patient received antibiotic cover in the form of a single parenteral injection of tobramycin (120 mg) given one hour pre-operatively. The incised stricture was calibrated using Lister's bougies and a catheter (18-22 FG) was left *in situ* for either a short term (1-7 days) or a long term (28 days). The patients were managed at home during these periods. Follow-up was by urine flow measurements immediately after removal of the catheter, at monthly intervals for 6 months and 3-monthly intervals thereafter. Stricture recurrence was taken as a fall in peak flow rate to less than 10 ml/s for a voided volume of more than 150 ml, at which time a further urethrotomy was performed.

Results

Pre-operative flow rates varied from 1 to 17.5 ml/s,

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.

Table 2 Unsatisfactory Urethrotomy and Subsequent Management

Prostatic obstruction	4	Transurethral resection (2)
Oedema and subsequent restricturing	3	Repeat urethrotomy (3)
Bladder neck dyssynergia	2	Bladder neck incision (2)
Failed urethrotomy	1	Urethroplasty (1)
Chronic retention	4	Repeat urethrotomy (2) (4 weeks' catheterisation)

of which all but 5 were below 10 ml/s: 38 patients (73%) had post-operative flow rates greater than 15 ml/s. In the remaining 14 patients (27%), the flow rates were below this level and deemed unsatisfactory. The causes of these poor flow rates are shown in Table 2. Further treatment has resulted in a peak flow greater than 15 ml/s in 10 of these cases (Table 2).

Forty-five patients have been followed up for longer than 3 months (range 13-86 weeks). The overall recurrence rate was 51%, which comprised 33% of the low treatment group and 71% of the high treatment group. In the low treatment group, there was a lower recurrence in those patients who were managed by long-term catheters but the same did not apply to the high treatment group (Table 3). All stricture recurrences in this series occurred within 12 months; 22% recurred within 1 month, 43% within 2 months and 74% within 6 months. The time to recurrence did not appear to be affected by the previous treatment: a mean of 17.4 weeks for the low treatment group compared with 16.7 weeks for the high treatment group. Patients with long-term catheters took longer to develop recurrence: a mean of 19.2 weeks for the long-term catheter group compared with 15.3 weeks for the short-term catheter group. However, the single recurrence with a long-term catheter in the low treatment group took 32 weeks to develop.

Restricturing has occurred in 23 patients and a further 53 urethrotomies have been required to maintain these patients with flow rates above 10 ml/s. Of the 16 patients who have been assessed with both long-term and short-term catheters, 11 had a longer recurrence-free period after long-term catheterisation which varied from 2 to 17 weeks and a mean of 8.7 weeks. In 2 patients with aggressive strictures, there was no difference and both showed recurrence within 4 weeks. The 3 patients who did better with short-term catheterisation did so only when this was a second urethrotomy which followed a previous urethrotomy with long-term catheterisation (Table 4). At the beginning of this study, a few patients were catheterised for only 24 to 48 h after urethrotomy. It was noticed that these patients, acting as their own controls, did much worse when compared with urethrotomy followed by longer periods of catheterisation (Table 5). After successive urethrotomies, the overall recurrence rate has been reduced from 51% after the first urethrotomy to 33% after the second to 29% after the third. This figure largely reflects the improvement shown by the low treatment cases. The recurrence rate for the high treatment cases

Table 3 Recurrence Rate

Total 23/45 (51%)	Low treatment 8/24 (33%)	LTC 1/9 (11%)
		STC 7/15 (47%)
	High treatment 15/21 (71%)	LTC 9/12 (75%)
		STC 6/9 (67%)

LTC = long-term catheter.
STC = short-term catheter.

Table 4 Comparison of LTC with STC in Individual Patients

Time to recurrence with LTC	*Longer*	*Same*	*Shorter*
Preceding STC	5	1	3
Following STC	6	1	0
Total	11	2	3

LTC = long-term catheter.
STC = short-term catheter.

Table 5 Effect of Early Removal of Catheter Showing that a Shorter Duration of Catheterisation was Followed by More Rapid Recurrence (Figures Circled)

	Patient A			*Patient B*		
Catheter duration (days)	27	1	6	1	3	27
Time to recurrence (weeks)	16	⑤	29	⑤	20	34

	Patient C				*Patient D*		
Catheter duration (days)	1	29	4	3	27	2	5
Time to recurrence (weeks)	④	8	8	15	20	⑨	20

Table 6 Effect of Repeat Urethrotomy on Recurrence Rate

Recurrence after urethrotomy	*After first*		*After second*		*After third*	
Low treatment strictures	8/24	(33%)	4/24	(17%)	3/24	(12%)
High treatment strictures	15/21	(71%)	10/18	(56%)	9/17	(53%)
Total	23/45	(51%)	14/42	(33%)	12/41	(29%)

is still above 50% in spite of a total of 41 urethrotomies in the 9 who continue to recur (Table 6). Of the 12 patients who continue to recur in spite of 3 or more urethrotomies, the recurrence-free period has improved in all 3 of the low treatment group by a mean of 17.6 weeks, but in only 3 out of 9 in the high treatment group by a mean of 10.6 weeks. There remain 6 patients who have not shown progressive improvement by repeated urethrotomy. It is of note that the 9 recurring cases in the high treatment group included all of the 5 patients in this series who had had previous urethroplasties and 7 of whom were cases of strictures following direct trauma.

The only complications in 105 urethrotomies were one false passage, 2 transient fevers which did not require additional treatment and one minor haemorrhage.

Discussion

The results of this study so far strongly suggest that the single most important factor affecting the prognosis following single or repeated urethrotomy is the extent and frequency of previous treatment, rather than the length of history, severity of symptoms, the site, the length or the number of strictures. The only other factors found to be associated with a bad prognosis were a history of previous urethroplasty, the finding of palpable scar tissue around the urethra and possibly stricture formation secondary to direct trauma. Catheterisation after urethrotomy seems to be important and this study found that a catheter duration of less than 3 days produced inferior results. Long-term catheterisation for 28 days has proved to be noticeably better in reducing recurrence in patients with low treatment strictures. The same has not been true of the high treatment strictures except in lengthening the recurrence-free period, but this seems insufficient to warrant the additional patient inconvenience.

The use of a urine flowmeter is essential to the satisfactory management of these patients. The immediate post-catheterisation flow rate is the only way of determining whether the urethrotomy has been successful. Failure to obtain a peak flow rate greater than 15 ml/s for a voided volume of 150 ml is an indication for further urodynamic studies to assess detrusor function and detect persistent outflow obstruction. Regular out-patient flow measurements are the only reliable non-invasive method of detecting stricture recurrence, since patients did not generally complain of urinary difficulties until their flow rates fell below 6 to 7 ml/s.

The point at which a stricture has been deemed to recur is an arbitrary decision. In this study, recurrence was taken as 10 ml/s and, in the presence of unimpaired detrusor function, this point was not reached until the stricture had contracted to a size of 10 to 12 FG, which was an easy size on which to perform repeat urethrotomy, especially if done under local anaesthesia. Early repeat urethrotomy is easier, the fibrous tissue is immature and softer to cut and the procedure appears to produce relatively less trauma to the urethra.

Although some of the patients with recurrent strictures claimed to be able to manage satisfactorily even though their flow rates were below 10 ml/s, one must consider the risks of complications produced by leaving a severely obstructed outflow tract. It has been clearly demonstrated that the residual urine starts to increase dramatically in patients with strictures when the peak flow rate falls below 6 ml/s (Nyman, 1976). Four patients in this series, all of whom had had a previous prostatectomy, had flow rates less than 15 ml/s after urethrotomy, which were shown urodynamically to be due to impaired detrusor function. Satisfactory flow rates were obtained in only 2 of them by combining early repeat urethrotomy, 4 to 6-week catheterisation and oral bethanecol in doses of 120 to 200 mg daily. It was found in these patients that if the peak flow could be maintained by the use of cholinergic drugs, the stricture took longer to recur.

The use of regular urine flow measurements to assess the length of the recurrence-free period has been able to demonstrate which strictures are not curable by direct vision urethrotomy. In this series, 2 who fell into this category have undergone urethroplasty; a longer follow-up is needed to determine the overall need for urethroplasty. Failure of direct vision urethrotomy in some of these high treatment strictures may reflect the aggressive nature of the lesion, but it is the authors' opinion that the previous treatment of strictures by repeated bouginage, particularly under general anaesthesia, adversely affects the results of subsequent urethrotomy. Thus we feel that any surgeon who treats urethral strictures should only do so with the availability of a direct vision urethrotome and a urine flowmeter.

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Urethrolysis in the Management of Females with Recurrent Frequency and Dysuria

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Summary—The symptomatic results of urethrolysis were assessed in 40 female patients with the urethral syndrome. A specific clinical group of patients was identified who obtained symptomatic relief following surgery and these were further analysed, using urodynamic studies, to assess how urethrolysis achieved this effect.

The urethral syndrome has been defined as recurrent episodes of frequent, painful micturition not associated with any abnormality of the female lower urinary tract. Such a definition includes a number of pathophysiological abnormalities including urinary infection and chronic urinary retention. Other factors which have been identified in the aetiology of the urethral syndrome are bladder instability and urethral hypersensitivity (Kiesswetter, 1977).

Although medical measures such as a change in pH, hormone therapy and antibiotics remain the commonest methods of treating the urethral syndrome, surgical treatment is sometimes required in persistent cases. The principal techniques employed are urethral dilatation, urethroplasty and urethrolysis. Urethrolysis was described by Richardson (1969) as an operation which was used in the treatment of the urethral syndrome, particularly in the United States.

The purposes of the present study were to establish the place of urethrolysis in the treatment of recurrent frequency and dysuria in the female and to identify how this operation achieved symptomatic improvement in some patients.

Patients and Methods

Forty female patients have been assessed in this study. All were referred because of recurrent episodes of frequency and dysuria which had been resistant to previous medical therapy and urethral dilatation. Detailed pre-operative and post-operative symptomatic assessment was obtained in each case and all patients underwent urethrolysis under general anaesthesia.

The patient (in the lithotomy position) was catheterised using a wide bore tube so as to outline the urethra. A transverse incision was made beneath the urethral meatus and extended laterally and posteriorly so as to reflect the anterior vaginal epithelium from the distal third of the urethra. A transverse incision was then made across the urethra approximately (as measured with the catheter) one-third of the distance from the meatus. (This incision should be deep enough to incorporate all of the periürethral tissue but not breach the mucosa.) The incision was then extended upwards along the side of the urethra to the urethral meatus. This flap of periurethral tissue was carefully shaved off the urethral mucosa and excised, leaving 2 ends of cut periurethral tissue on either side of the mucosa which now alone covered this segment of the distal urethra. The incision was closed with deep transverse mattress sutures and the vaginal mucosa closed with interrupted catgut stitches. The catheter was removed and the patient encouraged to void spontaneously.

The results of urethrolysis were assessed by the subjective patient response to the operation and also by objective means with frequency/volume charts completed by the patient and urodynamic studies. The urodynamic tests consisted of a free flow rate with residual urine estimation, urethral profilometry, and filling and voiding cystometry (Abrams, 1976).

Results

The 40 patients were divided into 4 separate groups. The first group comprised those in whom the symptoms of frequency and dysuria were associated with urinary incontinence. In the second and third groups these symptoms were associated with recurrent proven urinary infections or persistent

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residual urine respectively. The fourth group consisted of patients in whom the symptoms of frequency and dysuria occurred with any of the factors described above.

The patients' symptomatic response to urethrolysis is shown in Table 1, which compares the results of the operation in the 4 symptom groups. The results have been divided into 3 categories: *good*, where the patients were completely asymptomatic on post-operative assessment; *satisfactory*, where the patients were improved but still had some residual symptoms, and *poor*, when the patients showed no symptomatic improvement following surgery.

The results demonstrate that in those patients whose urinary symptoms were associated with incontinence, urethrolysis resulted in symptomatic improvement in only 14% of the cases treated. Similarly poor results were obtained in patients whose lower urinary tract symptoms were related to either recurrent proven urinary infection or increased residual urines. However, in patients with frequency and dysuria alone, urethrolysis resulted in an 87% improvement rate in symptomatology.

In order to assess more fully the effect of urethrolysis in the group of patients in which it appeared to achieve most success (isolated frequency and dysuria), these patients were subjected to a detailed pre-operative and post-operative analysis using frequency-volume charts and urodynamic studies. Of this group 20 cases were available for study in which both pre-operative and post-operative investigations were available, and these patients were analysed separately. Their mean age was 35.8 years, with an age range of 19 to 58 years. The mean length of time to the post-operative assessment was 10.7 months, with a range of 4 to 36 months. Analysis of the frequency-volume charts (Table 2) showed that in these patients there was an objective improvement in the degree of both frequency and nocturia which was statistically significant ($P<0.05$). Statistical analysis was performed using the Student's t-test. A comparison of the urodynamic findings following urethrolysis (Table 3) showed little in the way of change. However, there was a trend for the urine flow rate to increase along with a small increase in the cystometric bladder capacity. No alteration was demonstrated in the voiding detrusor pressures following surgery, but there was evidence of a fall in the maximum urethral pressures. This reduction was not, however, statistically significant.

Table 1 Urethrolysis in 40 Female Patients

		Symptomatic results		
		Good	*Satisfactory*	*Poor*
Frequency, dysuria, incontinence	(7)	(0%)	1 (14%)	6 (86%)
Recurrent urinary infection	(1)	(0%)	(0%)	1 (100%)
Persistent urinary retention	(3)	1 (33%)	(0%)	2 (66%)
Frequency, dysuria	(29)	17 (59%)	8 (28%)	4 (13%)

Discussion

These results confirm the clinical impression that urethrolysis is useful in the treatment of females with recurrent frequency and dysuria. However, the selection of patients is important if satisfactory results are to be obtained. Pre-operative assessment should be undertaken to determine that symptoms are not related either to bacteriologically confirmed urinary infection or to chronic urinary retention. Furthermore, it appears that this operation should not be undertaken in patients who also give a history of urinary incontinence, for in these cases improvement is rarely obtained and there is the added risk of exacerbation of the incontinence.

In this series, post-operative morbidity was low following urethrolysis. However, 2 patients complained of stress incontinence after surgery. In one case the incontinence responded to pelvic floor exercises but the other patient remains symptomatic. Both cases reveal failure of operative technique due to too extensive a resection of peri-urethral tissue.

Analysis of the urodynamic studies of the group of patients most likely to show improvement after urethrolysis has revealed a striking uniformity

Table 2 Urethrolysis in Recurrent Frequency and Dysuria

	Frequency/volume charts	
	Pre-operative	*Post-operative*
Frequency	10.6 (SD 3.6)	7.2 (SD 2.5)
Nocturia	1.83 (SD 1.7)	0.8 (SD 1.0)

Table 3 Urethrolysis in Recurrent Frequency and Dysuria

	Urodynamics	
	Pre-operative	*Post-operative*
Urine flow rate	13.3 (SD 7.5)	20.8 (SD 10.6) ml/s
Cystometric capacity	276.3 (SD 124.7)	328.7 (SD 163.9) ml
Detrusor pressure on voiding (PDet)	42.5 (SD 13.1)	42.9 (SD 14 8) cmH_2O
Maximal urethral pressure	78.2 (SD 32.9)	69.2 (SD 31.8) cmH_2O

of findings. Their bladders demonstrate small cystometric capacities and they are uniformly stable on filling cystometry. Furthermore, they exhibit low urinary flow rates with either low or normal detrusor contractions. Outflow obstruction has not been demonstrated in any case.

Following surgery, little in the way of improvement was noted in the urodynamic measurements apart from a lowering in urethral pressures, which probably related to the increased incidence of urinary incontinence following urethrolysis.

It remains unclear, therefore, exactly how urethrolysis achieves symptomatic improvement in these cases. Recent studies (Splatt and Weedon, 1981) have suggested that there is an increase in the fibrous tissue surrounding the distal urethra in patients with these symptoms, suggesting a possible obstructive aetiology, but our studies have failed to show such obstruction. Urinary infection is not a factor, nor is chronic urinary retention; none of our patients has an increased bladder capacity. This leaves urethral hypersensitivity as the final possibility and in a separate study we have confirmed that urethral hypersensitivity is important in the aetiology of such symptoms (Powell *et al.*, 1981). It is possible, therefore, that urethrolysis may produce its effect by causing a partial denervation of the distal urethra.

It is concluded that urethrolysis is a satisfactory method of treating difficult cases of frequency and dysuria in the female patient whose symptoms are not associated with urinary infection or incontinence. It is suggested that this operation may affect the sensitivity of the urethra which has previously been shown to be increased in this group of patients.

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A 10-year Prospective Study of Hypospadias Repair at Frenchay Hospital

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Summary—A 10-year prospective study of 91 cases of hypospadias treated in Bristol hospitals is reviewed.

By using only 3 basic repairs and a refined technique, which includes the use of magnification and fine instruments, the fistula rate has been markedly reduced in this series compared with that reported in 1976.

In a previous paper Smith *et al.* (1976) reported a retrospective study of hypospadias repair in Bristol hospitals that showed an unacceptably high incidence of complication and failure. As a result of that review a co-ordinated treatment programme using 3 basic repairs was instituted jointly by the Departments of Plastic Surgery and Urology. This paper reports the results of hypospadias repairs in 91 patients over the 10-year period January 1969 to December 1978.

One surgical team did one-stage repairs and the other team did 2-stage repairs for the purposes of comparison and evaluation. The following is an outline of the 3 types of repair used.

The Operations

For each of the 3 repairs preliminary urethral dilatation is performed to detect any meatal stenosis. Any chordee is released by making a transverse subcoronal incision and excising the dense fibrous chordee tissue from meatus to glans from one midlateral line to the other, exposing the blue colour of the corpora. If there is any doubt about the release of chordee a saline injection erection test is done.

The 2-Stage Byars Repair (Figs. 4-7)

The 2 stages, as illustrated by Smith *et al.* (1976), are performed between the ages of 3 and 5 years, before the child starts school.

The First Stage

This is commenced by urethral dilatation and chordee release as described above. The glans is split deeply in the ventral midline and the subcoronal incision is completed circumferentially. The 2 layers of the prepuce are carefully separated on their subcutaneous tissues and the unfolded prepuce is split longitudinally dorsally. The 2 flaps are brought ventrally and sutured into the cleft created in the glans. The adjacent flap edges are stitched together and to the underlying corpora in the midline from the meatus to glans tip. A foam and micropore dressing is applied to hold the flaps in position. On the fifth post-operative day the dressing is removed and the child goes home.

The Second Stage

This is performed not less than 6 months later. Urethral sounds are passed. A 10 FG suprapubic catheter is introduced by means of a trochar and cannula into the bladder previously distended with normal saline using a urethral catheter which is then removed.

The flap to be raised to create the new urethral tube is marked out over a 10 FG catheter. This flap is incised and raised at its edges so that it can be carefully tubed with a 6/0 Dexon continuous subcuticular suture, from proximal to distal end. The flap design adjacent to the meatus is such that a diverticulum is not produced (Townsend, 1975). Skin cover is provided by undermining the lateral penile skin which is closed in 2 layers, the subcuticular stitch being continuous.

On the tenth post-operative day the child is bathed to facilitate the removal of the micropore dressing and any meatal scabs. The suprapubic catheter is clamped, and removed once the child is passing urine *per urethram.*

The One-stage Repairs

These are performed when the child is 4 years of

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age. The flip flap repair is used for coronal and distal hypospadias, the Broadbent for midshaft and more proximal hypospadias.

Releasing the chordee increases the distance between the glans and meatus. If there is not sufficient non-hairy skin on the ventral penis to provide a flip flap long enough to reach the glans tip from its pivot point about 2 mm proximal to the meatus, a Broadbent repair is performed.

The post-operative procedure for removing dressings, meatal scabs and suprapubic catheter is the same as for the Byars repair above.

The Flip Flap Repair (Figs. 1-7)

After releasing the chordee, if any, the glans is cleft deeply in the ventral midline. The flip flap is outlined 10 mm wide based distally on the meatus. The flap is then raised and carefully tubed with a continuous subcuticular 6/0 Dexon suture. The flap is flipped over and sutured into the cleft in the glans. The suture line of the tubed flap lies deeply. Skin cover is provided by mobilising the penile skin laterally; if necessary a dorsal midline-releasing incision can be made to relieve any tension and a V-shaped corona-based flap of preputial lining can be set into the dorsal incision to make good the raw area.

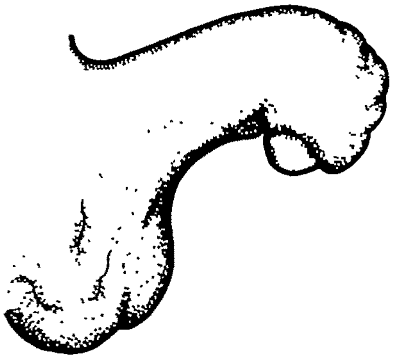

Fig. 1

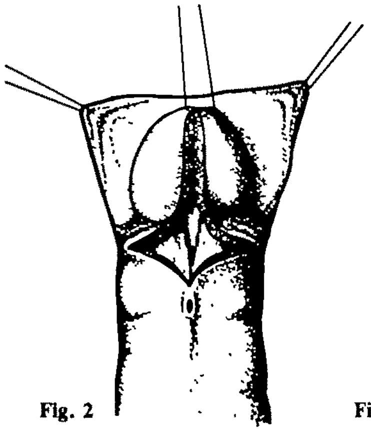

Fig. 2

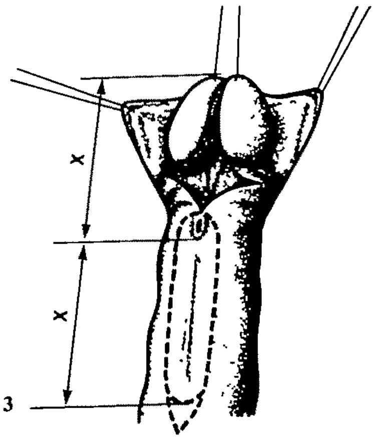

Fig. 3

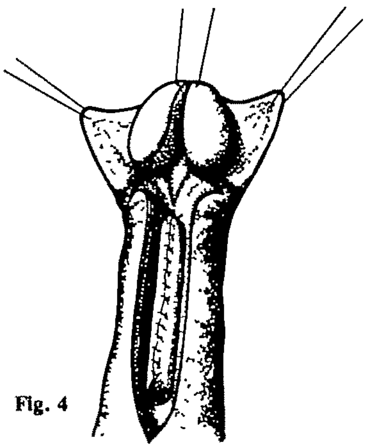

Fig. 4

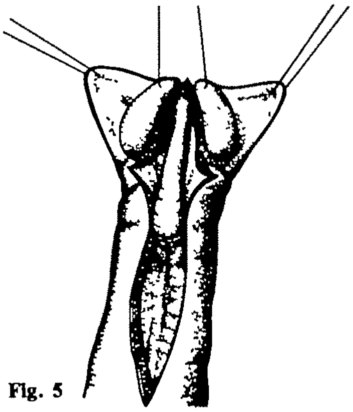

Fig. 5

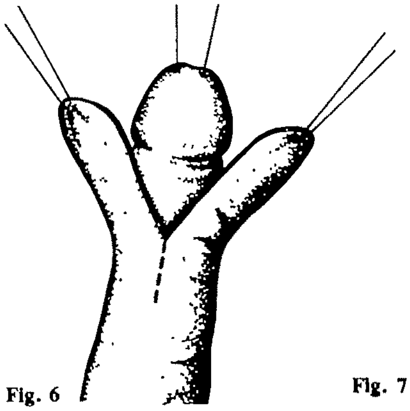

Fig. 6

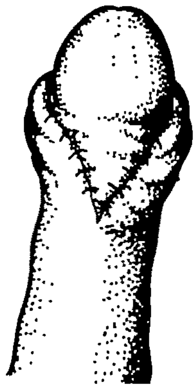

Fig. 7

Fig. 1 Distal hypospadias with chordee. "Flip flap repair" (Figs. 2-7). **Fig. 2** Release of chordee and creation of a deep cleft in the glands. **Fig. 3** The flap design shows the pivot point proximal to the meatus **Fig. 4** The flap is tubed. **Fig. 5** The tubed flap is "flipped" over to lie in the cleft glans. **Fig. 6** A dorsal-releasing incision is made in the prepuce. **Fig. 7** The corona based V-shaped flap of preputial lining is used to close the dorsal-releasing incision.

The Broadbent Repair (Figs. 8-13)

After releasing chordee, the glans is cleft deeply in the ventral midline. If there is insufficient non-hairy skin to provide a flip flap, the Broadbent type of flap is designed based on the meatus at its proximal end. The flap is 10 mm wide and passes around the penile shaft on to the dorsal prepuce beyond the midline. A pedicle of subcutaneous tissue containing the dorsal artery and vein is carefully preserved right to the tip of the flap. The pedicle is mobilised sufficiently to allow the flap to be sutured into the cleft glans and ventral midline after it is carefully tubed proximal to distal with a continuous subcuticular 6/0 Dexon suture. The remaining dorsal layer of the prepuce is split longitudinally to provide 2 skin flaps which are wrapped around to provide cover for the reconstructed urethra. The V flap of preputial lining based on the coronal sulcus is used to close the dorsal slit. Post-operative procedures are the same as for the other repairs.

Results (Table)

Ninety-one urethroplasties were performed between January 1969 and December 1978 and the results of 43 Byars, 33 flip flap and 15 Broadbent repairs are discussed.

For comparison, the urethroplasties can be divided into a proximal and a distal group. The

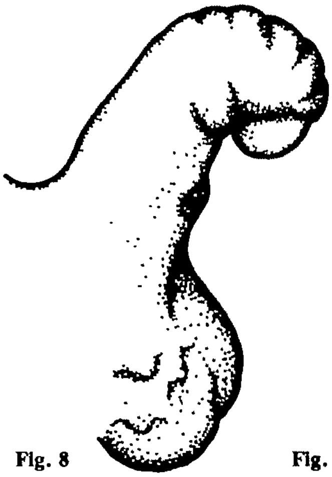
Fig. 8

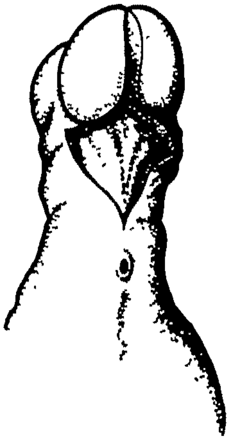
Fig. 9

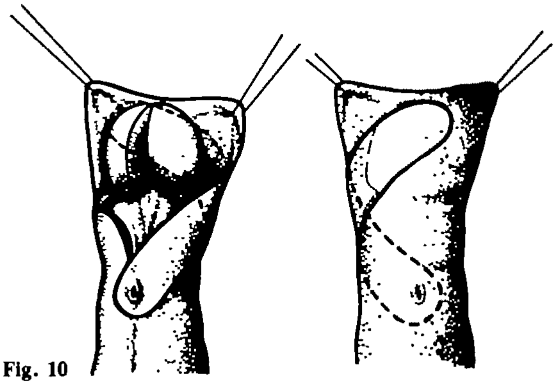
Fig. 10

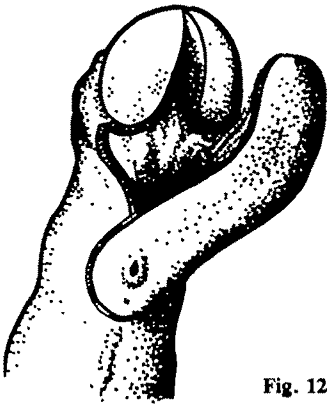
Fig. 11

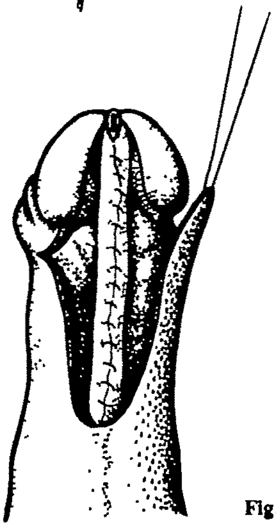
Fig. 12

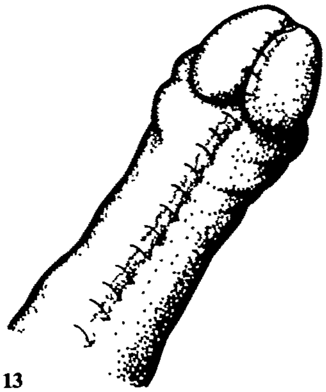
Fig. 13

Fig. 8 Midshaft hypospadias with chordee. "Broadbent repair" (Figs. 9-13). **Fig. 9** The chordee is released and a cleft is created in the glans. **Fig. 10** The flap is designed based on the meatus, passing over beyond the dorsal midline of the prepuce. **Fig. 11** The flap is raised, showing its full length subcutaneous pedicle. **Fig. 12** The flap is tubed. **Fig. 13** Closure by mobilising lateral flaps.

Table Fistula Rates for the 3 Types of Repair in this Series (91 Patients)

	Distal		*Proximal*	
	Byars	*Flip flap*	*Byars*	*Broadbent*
Cases	26	33	17	15
Fistulae	10	7	9	7
Fistula rate	38%	21%	53%	47%
Consultant fistula rate	2/5 40%	3/15 20%	2/5 40%	7/14 50%
Registrar fistula rate	8/16 50%	4/18 22%	7/12 58%	0/1 0%

proximal group contained 17 Byars and 15 Broadbent repairs. The distal group contained 26 Byars and 33 flip flap repairs. The fistula rate was taken as the main index of successful repair, although it is appreciated that other factors need to be considered.

In the proximal group the fistula rate was 53% for Byars repairs and 47% for Broadbent repairs. In the distal group the fistula rate was 38% for Byars and 21% for flip flap repairs. The consultant fistula rate was 40% for both proximal and distal Byars repairs, whereas the trainee fistula rates were 58 and 50% respectively. Consultants and trainees each had 20% fistula rates for flip flaps and the consultant fistula rate for the Broadbent repair was 50%.

Discussion

The aim of this prospective study was to find ways of reducing the complication rate of hypospadias repair in the Bristol hospitals. To achieve this 3 basic operations were used. One surgical team performed one-stage repairs, the other team performed 2-stage repairs.

The aim of urethroplasty is to create a new watertight distal urethra with a terminal meatus, from non-hair-bearing penile skin. The surplus dorsal preputial skin is used to provide skin cover ventrally or skin for the new urethra. Meticulous tissue handling, haemostasis and suturing are needed, using fine instruments and ×2 power magnifying loupes, and urine is diverted via a suprapubic catheter. It is clamped on the tenth post-operative day, after the child has been bathed to remove the micropore dressing and meatal scabs, for these can cause urinary obstruction and proximal fistula formation.

The rationalisation of operations to 3 basic procedures, urinary diversion, careful attention to surgical techniques and the post-operative removal of scabs have helped to reduce the fistula rate, more common with proximal than distal hypospadias, from 63% in the first series to 36% in this.

Trainees have the same fistula rate as their consultants for flip flap repairs, but do less well with the Byars 2-stage repair. Perhaps the trainees should begin their hypospadias surgery on cases suitable for flip flap repairs.

It is interesting to compare the numbers of operations per child for each type of repair. Cases treated with the 2-stage repair averaged 3 operations; the one-stage flip flap cases averaged 1.5 operations and the one-stage Broadbent cases averaged 2.6 operations. Thus there is a 50% chance that an extra operation will be needed for the Byars and Broadbent repairs, and a 20% chance for the flip flap repair The total time in hospital per case was about 8 days less for single stage than for 2-stage repairs. (Byars proximal 31 days, distal 26 days, Broadbent 23 days, flip flap 17 days.)

The achievement of good results in the treatment of hypospadias is a difficult and exacting exercise. The use of fine sutures and instruments and magnification helps to avoid piercing the epithelial lining of the new urethra when it is being tubed and reduces the chance of fistula formation. The use of non-hair-bearing penile skin, careful haemostasis with bipolar coagulation, urinary diversion and removal of meatal scabs have all helped to improve the results.

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Method, Indications and Results of Corpus Cavernosography

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Summary—Patients complaining of erectile dysfunction present with symptoms that are not readily reproduced for clinical observation. Corpus cavernosography provides a visual and radiographic diagnosis of the problem and may help in the understanding of the pathological process involved. Seventy-three cavernosograms were performed on 68 patients for symptoms relating to erectile deformities, both congenital and acquired, impotence and priapism. The indications, technique and results of corpus cavernosography are described.

The instillation of radio-opaque contrast into the corpora cavernosa of the penis was initially used to demonstrate the pelvic venous system (De La Pena, 1946). Motta (1956) used greater volumes of contrast and obtained excretory urograms with his venograms. May and Hirtl (1955) first described the radiographic abnormalities in the corpora themselves and suggested the usefulness of the technique in the investigation of conditions such as inflammation, injuries, priapism and tumour of the penis. Subsequently various techniques have been described for performing corpus cavernosography in the assessment of Peyronie's disease (Hamilton and Swann, 1967), priapism (Fitzpatrick, 1973; Ney *et al.*, 1976), genital trauma (Datta, 1977; Pliskow and Ohme, 1979) and impotence (Fitzpatrick and Fenimore Cooper, 1975). It is sometimes useful to be able to produce an artificial erection in order to assess the problem both visually and radiographically. In an attempt to ensure reproducibility and to facilitate our understanding of the pathophysiology of erectile disorders, a standardised method of corpus cavernosography has been adopted.

Patients and Methods

Seventy-three cavernosograms have been performed during the past 5 years on 68 men who presented with various complaints of erectile dysfunction to the St Peter's Hospitals. The patients' ages ranged from 14 to 72 years with an average age of 37 years.

Cavernosography was performed in 22 patients who had a variety of erectile deformities and in whom there was difficulty in reconciling the history and clinical findings. A further 46 patients underwent cavernosography on account of impaired potency. This represents but a small proportion of impotent men who have been studied (Morgan and Pryor, 1980) or treated in the clinic. In general, cavernosography was performed only if organic abnormalities of the vascular and erectile mechanism were suspected.

Cavernosography was performed under fluoroscopic control with the patient supine and with both radiologist and clinician present. No local or general anaesthesia was used. The skin was cleansed and a 19 gauge butterfly needle was inserted into one corpus cavernosum approximately 3 cm from the base of the penis. One hundred and twenty millilitres of 65% meglumine diatrizoate was diluted with 350 ml of saline and instilled using a Fenwall bag at a constant infusion pressure of 300 mmHg. The erectile tissue was opacified and a pseudo-erection produced. The clinician was able to observe the degree of tumescence and discuss with the patient the quality of erection and any deformity produced. Filling of both corpora occurred across the septum and the regularity of its outline and of the tunica albuginea were noted. Representative spot radiographs were taken during the examination, and in particular a straight film to demonstrate the pectinate septum and left and right oblique films. The needle was left in place on completion of the study until complete detumescence had occurred and local pressure was applied to the penis for a few minutes following its withdrawal. A tourniquet

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around the base of the penis was used in the first 10 cavernosograms performed but then discontinued unless it was considered important to demonstrate the corpus spongiosum. No sexual stimulation was applied during this series but in some patients a true erection did occur during the study.

Results

The normal cavernosogram showed rapid filling from one corpus across the midline pectinate septum to the opposite corpus. Before complete filling of the corpora was obtained venous drainage was readily seen at 15 to 20 s with the circumflex vessels draining from the base of the corpora upwards towards the deep dorsal vein of the penis. Some filling of the glans and corpus spongiosum occurred at this stage and within 30 s the iliac veins could be seen. As the corpora filled the contrast was homogeneous and outlined the thin pectinate septum and the smooth edged tunica albuginea which tapered to a convex termination anteriorly behind the glans and posteriorly with variable filling of the crura. A total of 120 to 300 ml of contrast was usually infused. In a few patients a true erection occurred during cavernosography with the superficial and deep veins closing.

The results may be discussed for 3 groups of patients.

Erectile Deformities

Twenty-two patients presented with a history of deformity on erection. The deformity had always been present in 5 patients.

Three patients showed no abnormality on clinical examination but their curvature was dramatically reproduced visually and radiographically. These patients were diagnosed as having a congenital curvature of the penis due to congenital disproportion of the tunica albuginea surrounding the corpora cavernosa.

In 2 patients the pseudo-erection was normal by both visual and radiographic inspection. A discussion of their normal appearances was sufficient to allay their anxieties.

The remaining 17 men presented with the symptoms associated with Peyronie's disease and in these the extent of erectile impairment was greater than expected from examination of the penis. The usual appearance of the cavernosogram in this group of patients with Peyronie's disease was again dramatic with most commonly a dorsal curvature. The plaques were often visible with widening of the septum, indentation or notching of the lateral margins of the tunica albuginea and with occasionally ring-like constriction around the corpora. Peyronie's disease is primarily a thickening of the tunica albuginea but in some patients there was extensive cavernous fibrosis. This is usually associated with impairment of the erection.

Erectile Impotence

Thirty-seven patients presented with the inability to obtain or maintain an erection sufficient for intercourse. This was due to a variety of factors, as shown in the Table.

Six with Peyronie's disease had undergone plaque excision and the dermal graft procedure 1 to 5 years previously. They complained of impaired quality of erections and their cavernosograms showed some irregularity beneath the dermal graft but more complete filling of the corpora than in the pre-operative cavernosograms. It was not felt that the impaired erection was due solely to the loss of erectile tissue.

Five patients gave a history of penile trauma and their cavernosograms showed filling defects due to cavernous fibrosis. These may be considered atypical cases of Peyronie's disease.

Two patients had sustained a severe pelvic fracture and their cavernosograms demonstrated the anatomical position of the crura which had been displaced. This was of assistance in planning their subsequent surgery.

The cavernosograms in 3 patients with primary impotence was normal and although the penis enlarged it did not adopt the "erect" position. In these patients it was possible to insert the examining finger between the symphysis pubis and the dorsum of the penis. It was possible to correct these suspensory ligament abnormalities of the penis (Pryor and Hill, 1979).

Two patients complained that the glans penis

Table Diagnosis in 37 Patients Presenting with Erectile Impotence

Abnormal		*Normal*	
Peyronie's syndrome	6	Diabetic	3
Post-penile trauma	5	Idiopathic	16
Post-fractured pelvis	2		
Suspensory ligament	3		
Spongiosal dysfunction	2		

was small and did not tumesce on erection. This was confirmed on infusion cavernosography even though the corpora cavernosa appeared normal.

In 19 men the cavernosograms were considered to be normal and the demonstration of this was often of therapeutic benefit to the patient.

Priapism

Nine patients presented with impotence following priapism. The 3 patients who had been treated by aspiration of the corpora cavernosa and the one who had had a corporo-spongiosal shunt all showed extremely poor filling of the cavernous spaces and in one patient only 5 ml of contrast could be introduced. The radiographic appearances demonstrated the extent of fibrosis within the corpora (Fig.) but the crura often remained normal.

In 3 patients who had primarily undergone a corporal saphenous bypass operation, and another following a corporal spongiosal shunt, all showed patency of the shunts which rapidly diverted the contrast away from the corpora into the large veins of the pelvis.

One patient had previously had a corporal spongiosal shunt performed for priapism, with good immediate decompression and a return of potency for 3 months. He presented again with a semi-erect painful penis and cavernosography demonstrated impaired venous outflow to the deep dorsal vein and some degree of distal cavernous fibrosis. A further corporal saphenous bypass was performed with improvement.

There were no allergic, systemic or local reactions due to the contrast material, but occasionally a minimal haematoma was noted by the patient. Although there have been reports of fibrosis in the corpora following cavernosography (Byström *et al.*, 1974), none were encountered in our patients, but the investigation should therefore be used with discretion.

Discussion

The ability to reproduce tumescence with an artificial erection is useful to assess the situation visually and radiographically. The presence of the clinician during the examination provides a useful opportunity to discuss the exact nature of the problem with the patient. This is particularly useful in patients with a minimal or absent deformity or abnormality. The choice of treatment may be influenced by the results of cavernosography, particularly when the deformity is greater than expected and there is significant impairment of cavernous filling.

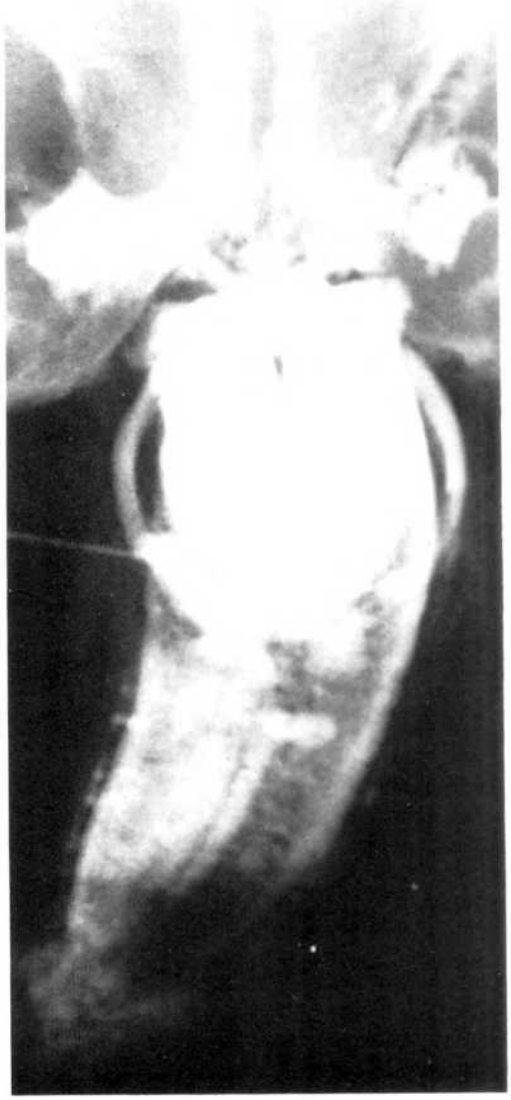

Fig. Cavernosogram following priapism showing good proximal but poor distal filling of corpora cavernosa, reflecting the extensive cavernous fibrosis within the corpora.

Cavernosography is seldom indicated in Peyronie's disease. It is indicated only if there is clinical doubt about the extent of the erectile problem and in particular when flaccidity of the distal penis is described. Cavernous fibrosis may result from arterial occlusion and may also be seen on cavernosograms following penile trauma (Pryor *et al.*, 1981). These patients usually require the implantation of a penile prosthesis.

In patients who sustained a severe injury to the pelvis with displacement of the crura, and in those who have suffered traumatic loss of the penis, cavernosography will define the corpora and facilitate the planning of reconstructive procedures.

Cavernosography has been used at this institute as part of the protocol for the investigation of impotence (Morgan and Pryor, 1980) but rarely provided useful information. In 3 patients it confirmed the diagnosis of an abnormality of the suspensory ligament of the penis and facilitated the recognition of this condition.

There have been reports of abnormal venous drainage of the corpora cavernosa causing impotence in the bull (Ashdown and Gilanpour, 1974) and in man. Ebbehøj and Wagner (1979) described 4 such patients and surgical correction of the "fistula" resulted in a return of potency in 3 men. The abnormal venous drainage was demonstrated only during sexual arousal when the increased arterial input produced sufficient outflow for the "fistula" to be visualised.

Priapism is one of the few true urological emergencies and inadequate or delayed treatment is often followed by the replacement of the corpora by fibrous tissue. This is readily visualised at cavernosography and enables the surgeon to assess the difficulty likely to be encountered during the insertion of a penile prosthesis. Some patients remain impotent even following successful surgical decompression of priapism and occasionally their venous shunts remain patent and are visualised on cavernosography. They may be surgically closed in an attempt to improve potency.

It has been suggested that the presence of competent deep dorsal venous valves in the penis assist in maintaining an erection (Fitzpatrick and Fenimore Cooper, 1975). This valve was noted in a number of cavernosograms but no diagnostic conclusions were based on its absence.

In conclusion, corpus cavernosography is a useful technique that provides a visual and radiographic reproduction of the problems relating to erectile dysfunction. Further studies with sexual stimulation during cavernosography may be useful in assessing the pathophysiology of erectile dysfunction and provide further information as to the causes of impotence.

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The Surgical Correction of Erectile Deformities of the Penis of 100 Men

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Summary—The Nesbit operation gave excellent results in 85% of 22 men with erectile deformities of the penis due to various congenital causes. The dermal graft procedure has been abandoned for the treatment of Peyronie's disease as a result of an unacceptably high incidence of post-operative erectile problems. The Nesbit technique successfully corrected the erectile deformity in 77% of 62 men with Peyronie's disease. Those patients with Peyronie's disease and erectile impairment due to cavernous fibrosis are best treated by the insertion of a penile prosthesis.

Erectile deformities of the penis are usually due to congenital abnormalities in younger men and to Peyronie's disease in the older age group. Nesbit (1965) described an operation to correct congenital erectile deformities by excision of ellipses of the tunica albuginea and there have subsequently been occasional case reports of this technique.

The surgical excision of the fibrous tissue in Peyronie's disease was generally unsuccessful as a result of further scarring. Bystrom *et al.* (1973) and Devine and Horton (1974) simultaneously described the dermal graft operation for Peyronie's disease and Kelami (1977) has modified the technique to utilise lypohilised human dura. Many surgeons found the dermal graft procedure unsatisfactory and prefer to implant a penile prosthesis (Raz *et al.* 1977). In 1976 we used the Nesbit operation to correct the erectile deformity in Peyronie's disease and the initial results were encouraging (Pryor and Fitzpatrick, 1979).

In this paper we report the results of surgical treatment of 22 men with congenital erectile deformity and 77 men with erectile deformity due to Peyronie's disease.

Patients and Methods

Twenty-two patients with congenital erectile deformities and one patient with chordee following a difficult urethroplasty were operated on using the Nesbit technique (Table 1). Patients with a "congenital short urethra", lateral deformity and chordee without hypospadias were under the age of 25 years when first seen. Their main complaint was anxiety due to the shape of their erect penis and only 4 patients had actually attempted intercourse. One patient was almost suicidal with worry about his penile malformation. Two patients who had previously been operated upon for the correction of hypospadias were found to have residual corporal deformity, although the urethra had been satisfactorily reconstructed. The mean length of follow-up of this group of patients was 18 months (range 4 months to 5 years).

Seventy-seven patients were operated upon for Peyronie's disease, *i.e.* approximately 10% of those patients attending the out-patient clinic with the disease. In all patients the disease had been present for at least one year prior to operation and they had received at least a 3-month course of Vitamin E 200 mg 3 times daily and often Potaba in addition. Surgery was performed only if the deformity of the penis was sufficient to make coitus difficult or impossible and was only undertaken when the disease appeared quiescent and the degree of deformity was stable. The mean age of the patients was 53 years (range 29 to 66) and the mean duration of disease was 26 months (range

Table 1 Aetiology of Deformity

Congenital short urethra	12
Congenital lateral deformity	5
Chordee without hypospadias	2
Post-hypospadias repair	2
Epispadias	1
Post-urethroplasty	1
Peyronie's disease	77

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1-10 years). Eight patients were treated using the dermal graft technique, 2 by the primary insertion of a penile prosthesis and 67 by the modified Nesbit technique, whereby only one ellipse of tunica albuginea was excised. The mean length of follow-up after the Nesbit operation was 21 months (range 6-36 months).

Results

The criteria used for assessing results are shown in Table 2.

Congenital Deformity

The results of the Nesbit operation for correction of congenital erectile deformities were very good (Table 3). The only bad result occurred in a patient with an epispadias which had been successfully closed as a child. He noted no improvement in the dorsal curvature of his penis. Moderate results were seen in 2 patients, one of whom had a tight frenulum post-operatively that caused pain during intercourse and this has now been divided. The other patient had a residual 15° lateral deformity but this presents no problems during intercourse.

Peyronie's Disease

Eight patients underwent excision of the plaque and a dermal graft procedure. The results were moderate in 3 patients and bad in 5. These 5 patients required the insertion of a Small Carrion penile implant as a secondary procedure because of severely impaired erections. Two further patients with erectile problems in addition to deformity had a penile implant as the initial treatment with moderate results.

Sixty-seven patients were operated upon using the modified Nesbit procedure and 5 of them have been lost to follow-up. Satisfactory results were achieved in 48 (77%) patients. Thirty-three patients had a straight penis, 19 a deformity of less than 30° but in 10 there was a residual deformity of more than 30° (Table 4). It is interesting to note that 7 out of these 10 patients still manage to have reasonably satisfactory intercourse. The mean length of follow-up for those patients with a straight penis was 16 months as opposed to 27 months for those with persisting deformity. It is possible, therefore, that with a longer period of follow-up the number of patients with a straight penis may decline slightly. An analysis of the bad results (Table 5) shows a variety of causes but progression or recurrence of the disease remains the largest cause. Reabsorbable sutures should not be used as they do not persist long enough to allow complete healing of the tunica albuginea.

Table 2 Assessment of Results

	Excellent	*Moderate*	*Bad*
Erection	Normal	Impaired	Absent
Deformity on erection	<10°	10°-30°	>30°
Penetration	Normal	Possible	Impossible
Coitus	Normal	Possible	Impossible

Table 3 Congenital Deformities: Results

Deformity	*Number*	*Excellent*	*Moderate*	*Bad*	*Unknown*
Congenital short urethra	12	10	—	—	2
Lateral deformity	5	4	1	—	—
Chordee	2	1	1	—	—
Hypospadias	2	2	—	—	—
Epispadias	1	—	—	1	—
Total	22	17	2	1	2

Discussion

Conservative management of patients with Peyronie's disease remains the cornerstone of treatment. There is no doubt that a large percentage of patients will obtain relief of pain and a smaller percentage resolution of plaque and improvement in deformity with time (Mira, 1980). In approximately 10% of patients there is persistence of the erectile deformity which may be sufficient to make intercourse difficult or impossible. Surgical correction of the deformity should then be undertaken but the results of all operations are far from satisfactory. The results of the dermal graft operation were unsatisfactory and this led many surgeons to use a penile prosthesis. The excellent results of the Nesbit technique in patients with congenital erectile deformities led to the use of

Table 4 Peyronie's Disease. Results of Nesbit Operation

Overall		*Deformity*	
Excellent	25 (40%)	Straight	33 (53%)
Moderate	23 (37%)	10-30°	19 (31%)
Bad	14 (23%)	30°	10 (16%)

Table 5 Peyronie's Disease. Analysis of Bad Results

Erectile failure	2
Pain	1
Dexon failure	2
Coital trauma	1
Progression/recurrence of disease	9

this technique in patients with Peyronie's disease. In this operation the plaque is not removed as it is more important to correct the functional abnormality. The Nesbit operation shortens the penis but this has not proved to be a problem as only one patient complained that he has been "robbed" of his penile length. Progression or recurrence of the disease remains the most important cause of failure but it has not been possible to predict in which patients this will occur.

The time since onset of the disease, the age at presentation, the presence of calcification or Dupuytren's contracture were similar in those with and without progression or recurrence of the disease. It is often difficult to distinguish between these 2 causes of failure.

It is concluded that the Nesbit technique is a simple operative procedure that gives good results in both congenital deformities of the penis and Peyronie's disease.

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Elective Delayed Excision of Bulky Para-aortic Lymph Node Metastases in Advanced Non-Seminoma Germ Cell Tumours of Testis

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Summary—Forty-one patients with advanced non-seminoma germ cell testicular tumours were treated by chemotherapy, with or without radiotherapy, followed by excision of residual para-aortic lymph node masses. All para-aortic metastases were initially greater than 2 cm, 35 were larger than 5 cm, and 9 were over 10 cm in diameter. Seven patients also had nodal deposits above the diaphragm and 18 had distant metastases.

The residual masses were excised completely in all except 3 cases. Residual malignancy was found in 7 (18%) of 38 operable cases; of these 7, only 2 remain alive and disease-free. In contrast, 28 (90%) of 31 operable cases with necrosis and fibrosis, or with fully differentiated teratoma, are alive and disease-free. Elevated serum markers were found in 6 of 9 cases with resectable or unresectable residual malignancy, but in only 1 of 32 who were tumour-free. Residual malignancy was found in 3 (9%) of 34 cases with normal marker levels. Malignancy was not found in any residual mass less than 4 cm diameter.

We conclude that excision of para-aortic lymph node masses should be electively delayed until serum markers become normal and until shrinkage of the mass has ceased. The presence of residual malignancy in the excised tissue then provides a clear indication for further chemotherapy.

The results of treatment of non-seminoma germ cell tumours (malignant teratomas) of testis are dependent upon the volume of malignant tissue at presentation: with bulky metastatic deposits the prognosis becomes less good, an effect which has been demonstrated both with radiotherapy (Tyrrell and Peckham, 1976) and, more recently, with chemotherapy (Peckham *et al.*, 1979). It appears that these treatments may be unable to destroy all elements of tumour in a large mass and it is probable that recurrence of disease may stem from persistent foci of malignant cells within the residual lump. The commonest sites for large volume metastases from testicular tumours are the para-aortic lymph nodes. Routine lymphadenectomy in early cases has been avoided at this hospital, since staging and treatment planning has been based on non-invasive imaging techniques together with measurement of serum markers and because our results have been comparable with those reported from centres practising routine node dissections (Peckham *et al.*, 1981).

However, recognition of the failure of chemotherapy and radiotherapy to sterilise completely a certain number of bulky metastases had led us to explore the use of electively delayed para-aortic lymphadenectomy for removal of residual lumps in this region which failed to resolve completely on treatment. It was recognised from the outset that in many cases there would be no residual malignancy in these masses, but considerable importance was attached to the accurate definition of the nature of these residues so that the subsequent course of the patient could be related to the histological findings. It was also hoped that, in a proportion of cases, late recurrence of disease in this site could be prevented.

Patients and Methods

Forty-one patients were investigated, staged and treated between 1976 and 1980 by methods which have been described in detail elsewhere (Peckham

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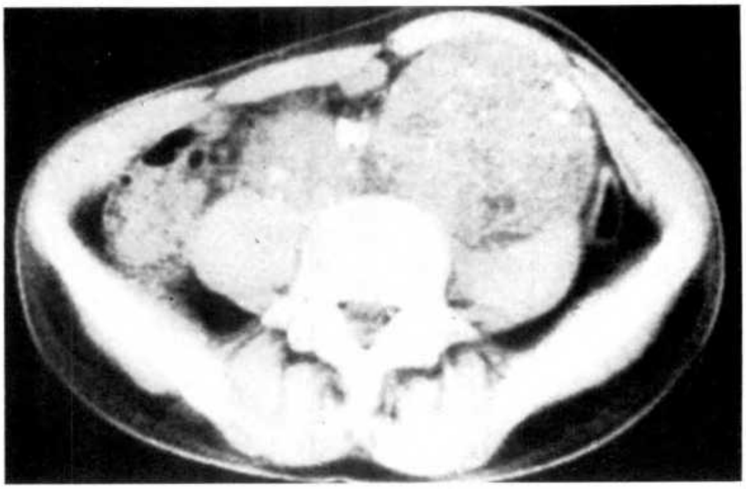
Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981.



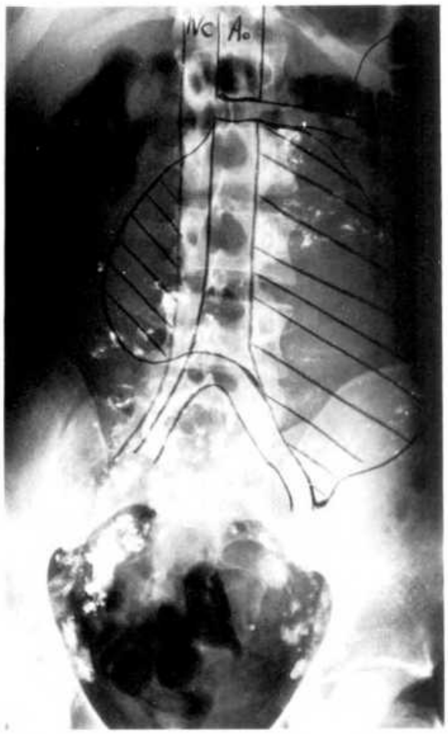


Fig. 1 (a) CT scan of large mass of para-aortic nodes lying on both sides of the great vessels. (b) "Scanogram" showing the extent of the mass and its relationship to vital structures. This information is essential in planning the surgical approach.

et al., 1981). These patients presented following orchiectomy with para-aortic lymph node masses greater than 2 cm in diameter; 35 were larger than 5 cm and 9 exceeded 10 cm as defined by lymphography, ultrasonography or computerised axial tomography. Seven patients also had nodes above the diaphragm and 18 had distant metastases: the distribution of the stage of the disease at presentation related to the histology of the primary tumours is shown in Table 1.

All patients were planned to receive at least 4 courses of chemotherapy, initially using a combination of vinblastine and bleomycin (VB—10 cases) (Samuels *et al.*, 1976), and subsequently employing a 3-drug regime comprising cis-platinum, vinblastine and bleomycin (PVB—19 cases) (Einhorn and Donohue, 1977). Nine patients received both VB and PVB during the period of transition from one regime to the other, and in 3 patients the vinblastine in the PVB regime was replaced by the epipodophyllotoxin VP 16-213. In 20 patients in whom there was no evidence of disease progression, radiotherapy (40 Gray in 4-5 weeks) was given to the para-aortic mass, commencing approximately 4 weeks after completion of chemotherapy. Nine other patients had had para-aortic irradiation elsewhere prior to relapse and referral to this unit. In 11 patients with very bulky disease in whom partial regression was evident after 4 courses of chemotherapy, a further 2 courses were given. Conversely, if massive disease showed little or no evidence of response and radiotherapy was technically difficult, the patients proceeded directly to surgery.

Table 1 Stage at Presentation Related to Histology of the Primary Tumour

Histology of primary tumour	*Stage*			*Total*
	II	*III*	*IV*	
MTI (teratocarcinoma)	7	3	9	19
MTU (embryonal carcinoma)	9	2	7	18
MTT (choriocarcinoma)		2	1	3
Seminoma with raised markers			1	1
Total	16	7	18	41

In all patients the position and extent of the residual masses were defined, 4 to 6 weeks after completion of chemotherapy and/or radiotherapy, by pyelography, ultrasonography or CT scanning (Hendry *et al.*, 1977; Husband *et al.*, 1979), and in some cases a "scanogram" was produced (Figs. 1 and 2). The patients were then explored and the masses excised using previously described techniques (Hendry *et al.*, 1980). A long midline incision was made in 31 cases, a Nagamatsu

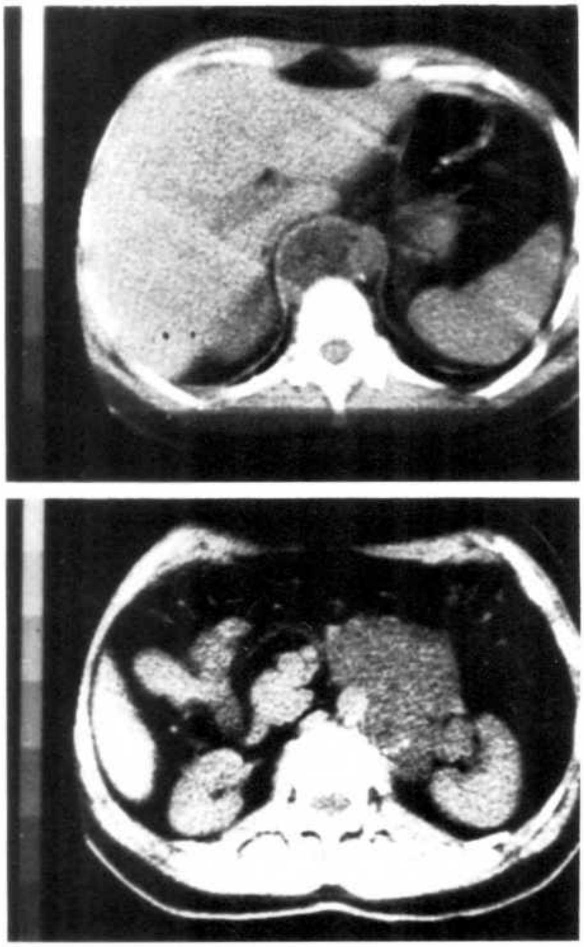


Fig. 2a CT scan showing large left-sided para-aortic mass and an additional mass higher up behind the right crus of the diaphragm.

incision in 2, and a thoraco-abdominal incision in 8. Small lung metastases were excised in 3 cases and mediastinal nodal masses in 4.

The excised tissue was examined histologically and the findings correlated with the initial histology, the size of the initial metastases and the residual lump, the level of tumour markers (alpha-feto protein and beta HCG) and the patients' survival. The patients have been followed for between 6 months and 4 years (median 19.6 months).

Results

The residual masses were excised completely in all except 3 cases. In 2 patients extensive, infiltrating, malignant tumour was encountered which could not be removed. In a third case completely necrotic tissue had infiltrated the femoral nerve roots and was incompletely removed; unfortunately, this patient died 10 days post-operatively of secondary haemorrhage, thus giving an operative mortality of 2.5%. The tumour had invaded the vena cava in 2 cases, and a sleeve of cava was resected with the tumour. The right external iliac artery was replaced by a Dacron graft in one case. Seven patients had removal of a poorly functioning ipsilateral kidney in continuity with the mass. One patient had a small pulmonary embolus, but no other serious post-operative complications were encountered.

In the masses excised completely, residual malignancy was found in 7 (18%) of the 38 cases. Overall, residual malignancy was found in 5 (24%) of 21 cases after chemotherapy alone (with or without previous radiotherapy), and 4 (20%) out of 20 after planned chemotherapy and radiotherapy. Differentiated teratoma was found in 18

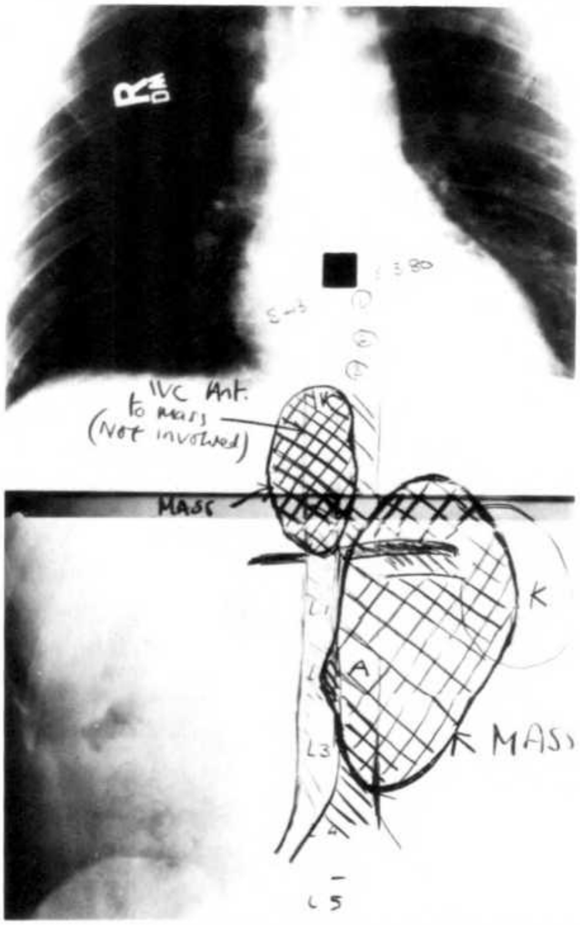


Fig. 2b The "scanogram" makes the situation clear for the surgeon.

Table 2 Histology of Excised Nodes Related to Histology of Primary Lesion

Histology of primary lesion	*Histology of excised nodes*		
	Necrosis, fibrosis	*Differentiated teratoma*	*Residual malignancy*
MTI (teratocarcinoma)	2	14	3
MTU (embryonal carcinoma)	9	4	5
MTT (choriocarcinoma)	1	2	
Seminoma with raised markers			1
Total	12	20	9

cases and this occurred most commonly when the primary tumour was teratocarcinoma (MTI) (Table 2). There was only fibrosis and necrotic tissue in 12 cases, 9 of which were originally embryonal carcinoma (MTU). Residual malignancy was not found in excised masses with a transverse diameter of less than 5 cm on presentation (stage II, III or IVB) or less than 4 cm at the time of surgery (Table 3). However, it was found in masses of all sizes above these dimensions, irrespective of the stage at presentation (Table 4).

Serum markers at the time of surgery were elevated in 6 of 9 cases with residual malignancy, but only in 1 of 32 without such disease. The correlation between elevated markers and the presence of residual malignancy in the nodes is highly significant (by Fisher's exact test, $P<0.01$) (Table 5).

Of the 38 patients in whom the mass was completely excised, 28 (90%) of 31 patients with fibrosis and necrosis, or differentiated teratoma, in the excised nodes are alive and disease-free, and 3 are alive with static disease. In contrast, 3 of 7 with residual malignancy in the completely excised nodes have died and another 2 are alive with disease. Only 2 are alive and disease-free. The correlation between disease-free survival and the histological findings in completely excised nodes is significant (by Fisher's exact test, $P<0.05$) (Table 6). By contrast, there was no correlation between disease-free survival and the size of the residual mass once its diameter exceeded 4 cm (Table 7). Most deaths occurred in patients presenting as Stage II (Table 8).

Table 3 Histology of Excised Nodes Related to Maximum Transverse Diameter of Residual Para-aortic Mass (cm)

Maximum diameter of residual mass	*Histology of excised nodes*		
	Necrosis, fibrosis	*Differentiated teratoma*	*Residual malignancy*
<4	8	5	
4-8	4	11	7
9+		4	2

Table 4 Histology of Excised Nodes Related to Stage Presentation

Stage	*Histology of excised nodes*		
	Necrosis, fibrosis	*Differentiated teratoma*	*Residual malignancy*
II	5	7	4
III	3	4	
IV	4	9	5

Discussion

The experience gained from these 41 patients has shown that almost all residual masses can be excised completely. Sometimes they can present serious technical problems, but these chiefly concern access, and with accurate pre-operative definition of the mass in relation to vital structures (Figs. 1 and 2) an appropriate surgical approach can be planned (McLorie and Skinner, 1980; Donohue and Rowland, 1981). Collaboration with a thoracic surgeon in cases with supradiaphragmatic residual masses, either pulmonary or mediastinal, has proved to be very valuable. Similarly, the pre-operative demonstration of caval involvement in one case allowed appropriate arrangements to be made for its removal. Few complications occurred, and no post-operative pulmonary

Table 5 Histology of Excised Nodes Related to Serum Marker Levels at the Time of Surgery

Serum marker levels at time of surgery	*Histology of excised nodes*		
	Necrosis, fibrosis	*Differentiated teratoma*	*Residual malignancy*
Normal	12	19	3
Raised		1	6

Table 6 Histology of Excised Nodes Related to Survival Status

Follow-up status	*Histology of excised nodes*		
	Necrosis, fibrosis	*Differentiated teratoma*	*Residual malignancy*
Alive and disease-free	10	18	2
Alive with disease	1	2	2
Dead	1*		5

* = post-operative death.

difficulties were encountered which could be ascribed to the previous bleomycin. Only 3 patients had masses which could not be removed completely. The patient who died post-operatively had presented with a paralysed leg due to femoral nerve root involvement; possibly the attempt to remove the mass completely was ill-advised, especially as the mass contained only necrotic tumour. The other 2 inoperable cases both had advancing disease with grossly elevated serum markers—we would not consider operating on such cases now. In a comparable series reported from the Memorial Hospital, New York, 11 of 48 cases were found to be inoperable after 2 or more courses of induction chemotherapy and all except one had residual malignancy (Vugrin *et al.*, 1981).

We found evidence of residual malignancy in 7 (18%) of 38 operable cases, which can be compared with 11 (30%) of 37 operable cases reported by Vugrin *et al.* (1981), and 9 (35%) of 26 similar cases reported by Donohue *et al.* (1980). There was little difference in the residual malignancy rate between those who had chemotherapy and radiotherapy (20%) and those who had only chemotherapy (24%). It is not possible to compare these data directly since case selection and amount of chemotherapy complicate interpretation of the results. On the one hand, patients with large residual masses tended to receive 6 rather than 4 cycles of chemotherapy and then proceed directly to surgery. On the other hand, 18 patients with para-aortic masses greater than 2 cm in diameter were treated with chemotherapy and radiotherapy alone since surgery was judged inessential. Increasingly we have tended to avoid surgery in patients with residual masses less than 3 cm in diameter at completion of chemotherapy and radiotherapy.

Table 7 Follow-up Status Related to Size of Mass at Surgery (cm)

Follow-up status	*Size of para-aortic mass at surgery*		
	<4	*4-8*	*>9*
Alive and disease-free	11	15	4
Alive with disease	2	3	
Dead		4	2

Table 8 Follow-up Status Related to Stage at Presentation

Follow-up status	*Stage*		
	II	*III*	*IV*
Alive and disease-free	10	6	14
Alive with disease	1	1	3
Dead	5		1

The serum marker levels gave a very accurate prediction of the presence of residual malignancy in the excised nodes, but it was not perfect. Of 34 patients with normal markers, 3 (9%) had residual malignancy. This incidence is much lower than that of 11 (29%) in 38 patients with negative markers reported by Vugrin *et al.* (1981). Nevertheless, it is clear that a minority of patients with normal markers after chemotherapy (with or without radiotherapy) have active malignant tissue in these residual lumps, and histological examination of this tissue provides a clear indication for further chemotherapy. It is important to note that residual malignancy has not been found so far in masses measuring less than 4 cm in greatest diameter prior to surgery. Preliminary data suggest that CT number may be a useful discriminant in deciding whether there is differentiated tissue or residual malignant disease (Husband *et al.*, unpublished observations). The prognosis for patients with active malignant tissue in the residual lump was poor since only 2 of 7 that were completely resected are alive and disease-free. This may be compared with 9 of 11 in the series reported by Vugrin *et al.* (1981), when the presence of residual malignancy was an indication for 2 further courses of chemotherapy, and 5 of 9 in the series described by Donohue *et al.* (1980), 2 of whom required extensive further chemotherapy.

It is possible to draw certain conclusions, as a result of this study, on the selection of patients and the optimum timing for removal of residual para-aortic masses with non-seminomatous germ cell tumours. The prognosis for patients with advancing disease and grossly elevated markers is poor and surgery is unlikely to influence the progression of the disease. Similarly, the persistence of elevated marker levels with a static residual lump is an indication for further chemotherapy, not for surgery. It is our present policy not to attempt excision of para-aortic nodal masses if the serum markers are elevated and to defer surgery in patients with normal markers until the mass has ceased to shrink. Then the presence of residual malignancy in the excised tissue provides a clear indication for further chemotherapy, since the operation itself is seldom successful in eradicating the residual malignancy completely. Whether excision of fully differentiated adult teratoma is therapeutically beneficial in the long term is not known. Overall, 30 (73%) of this group of 41 patients are alive and disease-free. This may be compared with 21 (80%) of 26 reported by Donohue *et al.* (1980), and 14 (70%) of 20 described by McLorie and Skinner (1980).

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Reversal of Vasectomy: the Effects of Sperm Antibodies on Subsequent Fertility

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Summary—Antisperm antibodies were measured in serum and seminal plasma in 130 males before and after vasectomy reversal and the occurrence of pregnancy was analysed in the partners of 77 who were followed for more than one year. Sperm-agglutinating antibodies were found in the serum of 79% of patients; seminal plasma antibodies were present in only 9.5% before reversal and this rose to 26% afterwards. Pregnancies occurred in the partners of 53% of those men who were trying to produce children. A pregnancy was significantly less likely when the pre-operative serum antisperm antibody titre was 512 or more, but no decrease in fertility was seen with titres below this. Several pregnancies were produced by patients with seminal plasma antibodies, but numbers and follow-up are too small to permit detailed analysis.

A randomised controlled trial of per-operative steroids showed that they produced no benefit. The antisperm antibodies associated with vasectomy reversal appear to differ fundamentally from those occurring in naturally subfertile males.

Serum antisperm antibodies develop in 60 to 80% of men following vasectomy (Ansbacher, 1973; Hellema and Rumke, 1978a; Rose and Lucas, 1979), but their effects on fertility following vasectomy reversal are poorly understood. Gupta *et al.* (1975) reported only 3 fertile men amongst 13 normospermic men after vasectomy reversal; these 3 men had serum sperm-agglutinating antibodies but no sperm-immobilizins and no seminal plasma antibodies. Sullivan and Howe (1977) found agglutinating antibodies in the serum of 48% of 29 men whose wives became pregnant, which was significantly less often than in 16 whose wives did not, of whom 94% had such antibodies.

The relation between pre- and post-vasectomy reversal antisperm antibodies and fertility was clarified considerably by Linnet *et al.* (1981), who showed that antibodies were detectable in seminal fluid of only 2 of 29 men before bilateral vasovasostomies, but were present in 10 men (34%) afterwards. Twenty of these men were trying to produce children: 11 pregnancies resulted among the 13 women whose men had no antibodies in seminal plasma, but only 1 among the 7 whose men had such antibody. This highly significant association established the relationship between *seminal plasma* antibodies after vasectomy reversal and fertility, but from these data a recommendation was made that *serum* sperm agglutinins should be measured before vasectomy reversal and used as a basis for counselling on the likelihood of restoration of fertility.

We have also been studying antisperm antibodies in serum and seminal plasma before and after vasectomy reversal, and in this report we present a preliminary analysis of our results which can be compared with the conclusions outlined above. Since there is evidence that leakage of sperms into the tissues at the time of vasovasostomy may stimulate antibody production and induce granuloma formation with fibrosis at the site of anastomosis (Hagan and Coffey, 1977), we conducted a prospective controlled trial of per-operative steroids to determine whether this therapy would prevent these effects.

Table 1 Concordance Between Serum Antisperm Antibody Tests

TAT=GAT within 2 titres	*TAT*>GAT (+type of agglutination)			
	≥2 titres	*T-T*	*H-H*	*T-T/H-H*
222	20	3	7	10

Read at the 37th Annual Meeting of the British Association of Urological Surgeons in London, July 1981

Table 2 Pre-reversal Antibody Status

Serum TAT titre	*Number of patients*	*Seminal plasma TAT titre* No. tested	0	4	8	16	32
Not done	9	4	4				
0	26	15	15				
4	5	2	2				
8	5	4	4				
16	4	2	2				
32	7	7	7				
64	11	9	9				
128	6	3	3				
256	16	11	11				
512	23	15	12	1	1	1	
≥1024	18	13	8	2	1	1	1
				3	2	2	1
Total	130	85	77	8/85 (9.5%)			

Table 4 Change in Serum Antisperm Antibodies Before and After Reversal

	Time after vasectomy reversal	*Change in serum TAT titre* Down ≥2	Unchanged	Up≥2
With steroids	1 week	1	23	1
	3 months	2	21	1
Without steroids	1 week	1	22	3
	3 months	4	17	4

Patients and Methods

Between September 1979 and December 1980, 130 vasectomised men underwent bilateral side-to-side vasovasostomies, using 6/0 Prolene and no splints (Hendry, 1979). Patients were randomised to receive either hydrocortisone 100 mg intramuscularly at the time of operation, then prednisolone 10 mg twice daily by mouth for 5 days, or no steroids.

Antisperm antibodies were measured in serial dilution by tray agglutination test (TAT) (Friberg, 1974), gelatin agglutination test (GAT) (Kibrick *et al.*, 1952) and micro-sperm immobilisation test (MIT) (Hellema and Rümke, 1978b). Serum samples were taken before, 1 week and 3 months after operation. Seminal plasma antibodies were measured before and 3 months after reversal; sperm counts were checked at 3 months, and at intervals thereafter. Since many of the patients lived a considerable distance from the 2 centres carrying out this procedure, not all follow-up specimens could be obtained; however, attempts were made to contact all patients to encourage them to send the semen samples and to enquire about the occurrence of pregnancy in their partners.

Table 3 Post-reversal Antibody Status (3 months or more)

Serum TAT titre	*Number of patients*	*Seminal plasma TAT titre* No. tested	0	4	8	16	32	≥64
Not done	71	13	11			2		
0	9	6	6					
4	0							
8	4	3	3					
16	0							
32	4	4	4					
64	9	7	7					
128	8	8	4		2		1	1
256	10	8	5			2		1
512	8	7	3	1		2		1
≥1024	7	5	2			1		2
				1	2	7	1	5
Total	130	61	45	16/61 (26%)				

Results

The interval between operation and follow-up was over 1 year in 77 cases and at least 6 months in all 130 patients. Antisperm antibody results have been analysed for all patients, but occurrence of pregnancies in their partners has been studied only in those followed for more than 1 year.

The results of TAT and GAT in serum coincided within 2 titres in 222 (92%) of 242 tests. In 20 the TAT was 2 or more titres higher than GAT: in 17 of these cases there was a significant element of head-to-head agglutination, which is only detected by TAT testing (Table 1). Since head-to-head agglutination is fairly common after vasectomy

Table 5 Change in Seminal Plasma Antisperm Antibodies

	Change in seminal plasma TAT titre No antibodies	Down ≥2	Unchanged	Up≥2
With steroids	22			3
Without steroids	13	2		6

Table 6 Results One Year or More After Vasectomy Reversal

	Total no.	*Information available*	*Sperm count*			*? Pregnancy*	
			0	*<20*	*⩾20 m/ml*	*Trying*	*Success*
Brighton	54	40	1	16	23	37	23 (62%)
Barts	23	19	3	6	10	16	5 (31%)

(Hellema and Rümke, 1978a), though rare in naturally subfertile males, the results of the TAT tests have been used in this analysis. The MIT results have not been included in this study.

The antisperm antibody results in serum and seminal plasma before vasectomy reversal are shown in Table 2. A positive result was obtained in the sera of 95 (79%) of 121 men tested. Seminal plasma antibodies were found in only 8 (9.5%) of 85 men tested, all of whom had serum titres of 512 or more. Overall, 41 (34%) of 121 men tested had serum titres of 512 or more. The corresponding figures 3 months or more after reversal are shown in Table 3. Only 61 patients have had seminal plasma tested at this time; however, it may be seen that a greater proportion—16 (26%)—had seminal plasma antibodies, which appeared at serum titres of 128 and higher.

Most of the serum antisperm antibody titres remained unchanged before and after reversal; a few went up and a few went down (Table 4). Rather less change was seen in patients given steroids. Nine patients showed a significant rise in seminal plasma antibodies, and in 3 more patients seminal plasma antibodies appeared transiently about 6 weeks after reversal and disappeared by 3 months (Table 5), an effect which has also been reported by Rümke and Hellema (1979). Fewer patients developed seminal plasma antibodies in the steroid treated group.

The results of follow-up sperm counts and pregnancies in the partners of those wanting children are shown in Tables 6 to 8, analysing only those followed for at least one year and excluding those lost to follow-up. Patency of the vasa was achieved in almost all cases (Table 6). The pregnancy rate for Brighton was 62% and for St Bartholomew's Hospital 31%: this disparity may be due to the fact that, in the latter institution, several repeat reversal procedures were included in the analysis and also, in the period under review, many of the procedures were done by a relatively inexperienced surgeon. The success rate was similar with and without steroids (Table 7). There was no evidence that pre-reversal antisperm antibody titre in serum had any predictive effect on the likelihood of pregnancy occurring in the partner until the serum titre reached 512 or more (Table 8). However, considerably fewer pregnancies were produced once this level was reached—a statistically significant difference which could be shown by chi-square testing using either TAT or GAT results (Tables 9a and b). So far, the numbers are small when post-reversal seminal plasma antibodies are considered (Table 10), but it should be noted that 2 pregnancies were produced with titres as high as 16. This will be the subject of further analysis in due course, when more patients have been followed for sufficient time.

A few patients exhibited an unusual course, and 2 are worthy of brief description. The first (Fig. 1) had no detectable antibodies before or immediately after reversal without steroids and a good sperm count was obtained; however, antisperm antibodies then appeared in both serum and seminal plasma and as the titre rose so the sperm count fell to nearly zero. The second patient (Fig. 2) started with a serum titre of 512 and seminal plasma titre of 8; after reversal without steroids a good count was obtained, the serum antibodies dropped, the seminal plasma antibodies disappeared and the wife became pregnant.

Table 7 Results One Year or More After Vasectomy Reversal

	Total no.	*Information available*	*Sperm count*			*? Pregnancy*	
			0	*<20*	*⩾20 m/ml*	*Trying*	*Success*
With steroids	34	28	2	8	18	29	15 (52%)
Without steroids	43	31	2	14	15	24	13 (54%)

Table 8 Results One Year or More After Vasectomy Reversal Related to Serum TAT Titre

Serum TAT titre	*Total no.*	*Information available*	*Sperm count*			*? Pregnancy*	
			0	*<20*	*≥20 m/ml*	*Trying*	*Success*
<32	21	15	2	4	9	16	9 (56%)
32-256	28	24		10	14	15	11 (73%)
≥512	24	17	1	7	9	20	7 (35%)

Discussion

These results confirm that agglutinating antisperm antibodies can be detected in the serum of over 70% of men following vasectomy. The observation that antibodies can be detected only in seminal plasma when the serum titre is 512 or more is entirely in accordance with the collected results summarised by Rümke (1978). This is quite different from naturally subfertile males, of whom about one-quarter have seminal plasma antibodies at a serum titre of 32, and over half have such antibodies with serum titres of 64. Rümke (1978) interpreted this distinction between vasectomised and naturally infertile males as being due to lack of locally produced antibody in the vasectomised males—their seminal plasma antibody prior to reversal is simply transudation from the circulation and hence is detected only with high serum titres. However, following reconnection, seminal plasma antibody appeared in substantially more patients, suggesting that this antibody was being produced in the epididymes or testes.

Table 9a Serum TAT Titre and Success of Vasectomy Reversal

Serum TAT titre	*Pregnancy*	
	No	*Yes*
0-256	11	20
512-1024+	13	7

($\chi^2 = 4.25$; $P < 0.05$)

Table 9b Serum GAT Titre and Success of Vasectomy Reversal

Serum GAT titre	*Pregnancy*	
	No	*Yes*
0-256	14	23
512-1024+	10	4

($\chi^2 = 4.6$; $P < 0.05$)

We found no relationship between pre-reversal serum spermagglutination titres and production of pregnancies in the partners until the serum titres reached 512 or more, when the decreased likelihood of fertility became significant using either serum TAT or GAT as the indicator. Linnet *et al.* (1981) suggested that a pre-operative serum titre above 64 should be used as the level above which seminal plasma antibodies could be expected to appear after reversal, and hence implied that this level should be used in counselling patients as that above which diminished fertility could be expected. Our results suggest that this is too low and show that a good result can be expected with pre-operative serum titres up to and including 256. Furthermore, the reduction in fertility that occurred with titres of 512 or more was only relative and 35% of these men were still able to produce pregnancies. Our experience, so far, has not shown that the presence of seminal plasma antibodies following vasectomy reversal is necessarily associated with poor fertility—2 of our patients produced pregnancies with seminal plasma titres of 16. This would be exceptionally unlikely to occur with naturally infertile males, and this distinction may be due to the antibodies being of a different type. Most of the antibody produced after vasec-

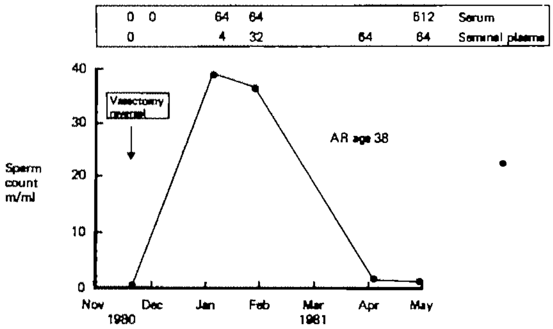

Fig. 1 Sperm counts and antisperm antibody titres in serum and seminal plasma before and after vasectomy reversal; note that antisperm antibodies were absent before reversal and that an initially good sperm count fell as the titre of antibody rose.

Table 10 Seminal Plasma Antisperm Antibodies and Success of Vasectomy Reversal

Seminal plasma TAT titre	*Total no.*	*Information available*	*Sperm count*			*? Pregnancy*	
			0	*<20*	*≥20 m/ml*	*Trying*	*Success*
0	47	41	3	14	24	33	15 (45%)
4-16	10	6		2	4	6	3
>16	2	2		2		1	0

tomy is IgG and some may transude into the seminal plasma, whereas in naturally infertile males the seminal plasma antibody is probably produced locally in the prostate or seminal vesicles as IgA, and accompanied by antibodies in the serum which are IgG (Rümke, 1978). Jager *et al.* (1980) showed that the shaking phenomenon produced by sperm-cervical mucus interaction, which indicates interference with normal sperm progression in the female genital tract, occurs only when sperms have IgA on their surface, and does not occur when the antibody is purely IgG. This may account for the apparently fundamental difference between the effects of antisperm antibodies in vasectomised and naturally infertile males.

The vasectomised man with a serum titre of 512 or more appears to be statistically less likely to have a successful result than a man with a lower titre, but this is not absolute and Figure 2 illustrates clearly that following reversal the antibodies may subside spontaneously and a pregnancy may be achieved. On the other hand, a man with no antibodies before reversal may develop them afterwards, apparently immunised by the procedure, and an initially good sperm count can then deteriorate—a phenomenon also documented by Marshall (1978). It is difficult to dissociate the development of antibodies from the fall in sperm count and it is probable that the antibodies caused the fall, especially since there were none in the pre-operatively totally obstructed state.

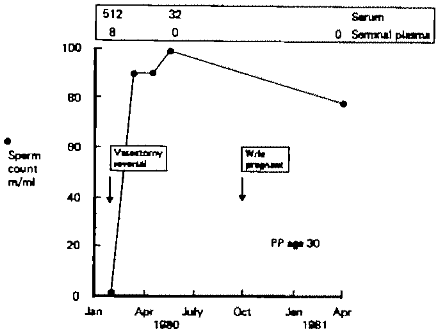

Fig. 2 Sperm counts and antisperm antibody titres in serum and seminal plasma before and after vasectomy reversal. The antibody titres fell profoundly after reversal and the wife became pregnant.

It is a mistake to generalise in assessing the likely effects of antisperm antibodies on vasectomy reversal. Antisperm antibody titres may go up or down after reversal and it is not possible to predict which will occur in an individual patient. We believe that counselling on vasectomy reversal should not be influenced by pre-operative antisperm antibody results; however, these should be estimated and the type of antibody on the spermatozoa should be defined, if the results of surgery are unexpectedly poor or if the wife fails to become pregnant after a reasonable time—perhaps one year.

Per-operative steroids have not been shown to confer any significant benefit compared with untreated controls.

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The Clinical Application of Electron Microscopy and the Heterologous Ova Penetration Test to the Assessment of Spermatozoa from Infertile Men

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Summary—Ultrastructural studies of spermatozoa from men whose spermatozoa repeatedly had shown poor motility demonstrated an increase in morphological abnormalities. This was considered significant in the 8 men in whom all of the spermatozoa were abnormal and probably significant in those where more than 90% were abnormal (9 men). Spermatozoa from 15 fertile men adhered to and penetrated 60% of hamster oocytes, whereas those from infertile men, with both normal and poor semen quality, failed to adhere or penetrate. The heterologous sperm penetration test offers a new approach to the assessment of semen quality in infertile men.

Investigation of the male partner of an infertile marriage aims to establish any cause for infertility in order that the couple may be accurately counselled and advised as to the availability of treatment or whether they should consider artificial insemination with donor semen. No cause for infertility is detected in many couples but each year it becomes possible to identify abnormalities in an increasing proportion of patients. This paper is a report of 2 techniques which have been used to evaluate the semen of infertile men.

The ultrastructure of spermatozoa, and well-known anomalies and malformations were classified by David *et al.* (1975). A small number of patients have specific ultrastructural abnormalities, such as absent acrosomal caps (Schirren *et al*, 1971), short tails (Baccetti *et al.*, 1975), or lack of dynein arms in the tail (Afzelius *et al.*, 1975). More recently de Cassaye *et al.* (1980) have reported their findings in asthenozoospermia. This paper is less concerned with the morphological abnormalities but with the percentage of abnormal spermatozoa in those patients with poor sperm motility.

The routine assessment of the quality of semen gives a very poor correlation with the fertility of the patient. The lack of a measure for the fertilising ability of spermatozoa, other than by conception rates, has led to many difficulties in the assessment of fertility. Yanagimachi *et al.* (1976) described the technique whereby human spermatozoa were tested for their ability to penetrate zona pellucida-free hamster ova. This dynamic test offers a means for assessing the fertility of a patient and the initial results (Rogers *et al.*, 1979; Hall *et al.*, 1980; Overstreet *et al.*, 1980) certainly suggest that this is possible. This paper reports our initial findings.

Methods

Samples of semen were produced by masturbation within the hospital, preferably after 3 days of sexual continence, and collected into sterile non-toxic plastic containers. The aliquot of freshly liquefied semen that was to be used for electron microscopy was first concentrated by centrifugation (1500 rpm). The spermatozoa-free supernatant was discarded and the remaining fluid mixed with Karnovsky's fixative (pH 7.4) overnight at 4°C. Next morning the spermatozoa were washed 3 times for 30 min in 0.1 M. cacodylate buffer (pH 7.4) and then post-fixed in 1% veronal buffered osmium tetroxide (pH 7.4) for 2 h. They were then washed in distilled water, resuspended in 10% bovine serum albumen and fixed overnight at 4°C. One-millimetre cubes of material were rapidly dehydrated through a graded series of acetone and resin embedded overnight. Polymerisation took place at 100°C for 5 h. Survey sections for light microscopy, 1 μm in thickness,

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were cut with glass knives on an LKB Ultratome and stained with 1% toluidine blue in 1% borax. Sections for electron microscopy, of pale gold interference colour, were cut with diamond knives, stained in uranyl acetate and Reynold's lead citrate, and examined with an AEI 6M transmission electron microscope at an accelerating voltage of 80 kV.

The full techniques of the heterologous ova penetration test for human spermatozoa has been described elsewhere (Tyler, 1981). In brief, 0.5 ml of semen was layered beneath the culture medium. In those men with poor quality semen the spermatozoa were concentrated by centrifugation and resuspension. The prepared spermatozoa were capacitated overnight (0.5 ml aliquots at 37°C) in small tightly stoppered sterile containers. Ova were collected from superovulated immature hamsters (mesocricetus auratus) and stripped of their cumulus and the zona pellucida. They were mixed with spermatozoa which had been prepared and capacitated in "BWW" medium. The spermatozoa were incubated with approximately 35 zona-free ova and examined 2.5 h later using Nomarski optics at a magnification of 400. The number of attached spermatozoa per oocyte was scored as zero, less than 5 or more than 5. A swelling sperm head or male pronuclei connected to a visible sperm tail were considered positive for penetration of an ovum.

Results

Ultrastructural Studies

The ultrastructural studies were performed on 5 normal volunteers and 50 patients with prolonged infertility and poor sperm motility on routine testing. The head, mid and tail pieces of the spermatozoa were assessed for normality and the proportion of abnormal forms scored. Table 1 shows the incidence of sperm abnormality in normal subjects.

From these data it was decided that in the normal individuals ultrastructural abnormalities occurred in up to 40% of head pieces, 60% of mid pieces and 40% of tail pieces. Forty-nine (98%) of the infertile men showed an increased number of abnormal spermatozoa: 30 (60%) had increased abnormality of the head piece, 39 of the mid piece, 41 of the tail piece. It is perhaps of significance that all of the tail pieces were considered abnormal in those patients with less than 30% of motile spermatozoa. Table 2 shows that in 8 patients all of the spermatozoa showed abnormalities of the head (1), mid piece (8) or tail pieces (4). Specific ultrastructural abnormalities such as lack of dynein arms were not seen in any patient.

Table 1 Ultrastructural Abnormalities of Spermatozoa 5 Normal Volunteers

Patient	*Incidence of abnormal spermatozoa (%)*		
	Head piece	*Mid piece*	*Tail piece*
1	40	59	34
2	36	56	45
3	34	29	24
4	21	46	26
5	22	42	25
Average ± S.D.	31 ± 8	46 ± 11	31 ± 8
"Normality"	<40	<60	<40

Heterologous Penetration Test

This was carried out on 3 groups of patients. The first group consisted of 15 fertile men with normal quality semen (Group I), whilst the second group consisted of 15 men with long-standing infertility but with normal quality semen. There was no significant difference between the various parameters of spermogram in these 2 groups. The third group of patients consisted of 9 patients with long-standing infertility and poor quality semen.

The results of these 3 groups are shown in Table 3. It is at once apparent that whereas the spermatozoa from Group I showed good attachment to the ova and sperm penetrated 284 or 467 ova (59.7%), in the infertile patients (Groups II and III) there was little attachment of the spermatozoa to the ova and the spermatozoa penetrated only 2 and 1% of ova respectively.

Table 2 Number of Patients with Grossly Abnormal Ultrastructural Morphology

Site	*100% abnormal*	*>90% abnormal*
Head piece	—	1
Mid piece	5	8
Tail piece	5	4
Total number of patients	8	9

Table 3 The Penetration of Zona-free Hamster Oocytes by Human Spermatozoa

Group	*Semen quality*	*Number*	*Mean number oocytes/ patient*	*Attachment*	*Penetration*
I Fertile men	Normal	15	31.7	+ +	284/476 (60%)
II Infertile men	Normal	15	39.1	+	11/586 (2%)
III Infertile men	Poor semen	9	33.3	0/±	4/300 (1%)

Attachment: >5 sperm/oocyte = + +.
1-5 sperms/oocyte = +.

Discussion

De Cassaye *et al.* (1980) stated that 60 to 70% of spermatozoa were of normal shape and that at the most 30 to 40% of cells showed minor defects. Our findings in the 5 normal volunteers showed abnormalities in up to 40% of the head and tail pieces and up to 60% of the mid pieces. The high incidence of ultrastructural abnormalities in patients with long-standing defects in sperm motility is not surprising. Many immobile spermatozoa are dead and the prolonged method of fixation may damage additional spermatozoa.

We believe that ultrastructural abnormalities were of undoubted significance in the 8 patients where at least one piece of all of the spermatozoa was abnormal and of probable significance in the 9 patients where over 90% of spermatozoa were abnormal. The abnormalities were not specific and were considered to be irreversible in patients with long-standing motility problems and no recent event which might interfere with sperm motility. Such patients should be counselled as to the poor prognosis and advised with regard to artificial insemination of the wife with donor sperm.

The ability of human spermatozoa to penetrate the vitelline membrane of hamster oocytes offers an *in vitro* opportunity to study the fertility of patients. The initial reports have been concerned with methodology, and the importance of sperm motility was demonstrated by Binor *et al.* (1980). In the present study the spermatozoa from infertile men, with both normal and poor quality semen, failed to show attachment or penetration of the ova. However, Hall (1981) found that only 32% of 25 infertile men with "normal" semen gave poor results with this test.

The ability of the sperm penetration of hamster oocytes test to discriminate between fertile and infertile men offers exciting prospects for the future management of infertile couples. This investigation will remain a research tool in view of the complexities of preparing zona-free hamster oocytes, although the use of cold preserved oocytes may increase its availability.

A full evaluation of the factors influencing the adherence and penetration of spermatozoa to the oocyte is currently being evaluated in many laboratories. An additional advantage of the test is that it may remove the need to assess male fertility drug trials by cumulative conception rates, since these are subject to many variables that are difficult to control.

Ultrastructural examination of spermatozoa revealed that poor sperm motility was associated with a high incidence of abnormalities. Patients with long-standing motility problems and ultrastructural abnormalities of all of the spermatozoa should be advised of the poor prognosis and artificial insemination with donor semen recommended. The heterologous sperm penetration test utilising zona-free hamster oocytes offers a new and exciting method for recognising infertile men and may be of value in assessing treatment and providing further knowledge concerning the pathophysiology of human fertility.

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The Long-Term Results of Surgery for Obstructive Azoospermia

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Summary—Thirty azoospermic patients with normal testes and normal serum FSH levels had scrotal exploration with photographic record of the appearance of the epididymes and vasography; bilateral epididymovasostomies were done if possible, with vasovasostomies if there were coexisting vasal blocks. Follow-up studies showed no success when the epididymes were empty (Type 1), when the vasa were absent or malformed (Type 2), or when tubular dilatation was confined to the heads of the epididymes; all of the latter cases had coexisting sinusitis, bronchitis or bronchiectasis (Type 4—Young's syndrome). Five patients with post-inflammatory disease had epididymes distended down to their tails (Type 3), and 3 also had vasal blocks. Three achieved sperm counts greater than 10 million per ml and impregnated their wives. Ten of 16 vasectomy reversals done by a similar side-to-side technique were successful.

A simple classification of obstructive azoospermia is described and it is concluded that in about 50% of cases the underlying cause of failure in sperm transport remains obscure.

In 1931, Hagner reported 19 successful epididymovasostomies in 31 assessable patients with azoospermia, 12 of whom subsequently fathered children. Hanley (1955) pointed out that the success rate in those with acquired post-inflammatory blocks was much higher than in those with congenital defects, ultimately defined as 65 and 3% respectively in an analysis of 400 men with azoospermia (Hanley and Hodges, 1968). It was concluded that there was a fundamental difference in the anatomy and physiology of the 2 groups, rather than any surgical or technical fault, to account for this difference. Schoysman (1978) analysed the results of more than 320 epididymovasostomies with follow-up in 260 patients: patency rate of one year was 54% and 18% of wives became pregnant. It was recognised that the best results were obtained when the anastomoses were done low down in the epididymes and it was suggested that this allowed better maturation of the spermatozoa. The importance of long-term follow-up was emphasised: cases were cited wherein a negative sperm count was recorded 2 months after operation and yet a good result was ultimately achieved and in some patients the ejaculate became positive only after 8 months.

In order to define the relationship between the aetiology of the azoospermia, the findings at scrotal exploration, and the ultimate success or failure of epididymovasostomy, long-term follow-up studies have been completed in 30 patients, whose investigations at the time of surgery and preliminary results were described previously (Hendry *et al.*, 1978). As a result, a system of classification of obstructive azoospermia is outlined, based on the findings in the epididymes, vasa and testes at operation. From this, the aetiological category can be defined and the likely prognosis deduced. Sixteen patients who underwent vasectomy reversal in the same period by a similar technique of anastomosis served as surgical controls.

Patients and Methods

Thirty men with azoospermia, normal testes and normal serum FSH levels were investigated as previously described (Hendry *et al.*, 1978). The scrotum was opened by a midline incision, the testes delivered and the vaginal spaces opened. The epididymes were examined and photographed. If the epididymis was empty a testicular biopsy was taken and nothing further was done. Provided that the epididymis contained distended tubules, attention was turned to the vasa. If they were absent, nothing further was done. If they were present, the vas was picked up across the

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tunica vaginalis and a short longitudinal incision was made. The lumen was cannulated with a size 2 FG intravenous cannula (Portex) and 5 ml 25% Hypaque injected before taking a vasogram X-ray film. The epididymis was then incised over the lowest part containing dilated tubules and side-to-side epididymovasostomy was completed with a continuous suture of 6/0 Prolene and no splint. If vasography showed a block in the vas, the area was explored through a separate incision and the block was corrected by division of the vas and side-to-side vasovasostomy with 6/0 Prolene. The same overlapping technique with side-to-side anastomosis using 6/0 Prolene and no splint was used for bilateral vasovasostomies in 16 patients undergoing vasectomy reversal in the same period. All patients wore a scrotal support lined with cotton wool for 7 days and remained in bed for 3 days.

Follow-up sperm counts were done at intervals between 3 months and 3 years after operation and enquiry was made about pregnancy in the wife. For the purposes of this study the follow-up results have been compared with the photographs taken of the epididymes at operation.

Results

The patients remain in the same groups as in the previous report, with one exception that will be described.

Group 1—Empty Epididymes (3 cases)

All patients remained azoospermic—testicular biopsy showed impaired spermatogenesis in 2 cases, one of which had a pituitary tumour.

Group 2—Malformed Vasa (7 cases)

A few sperms appeared after unilateral epididymovasostomy in one patient whose only vas was not connected to the epididymis. All other patients had absent vasa and remained azoospermic.

Group 3—Post Inflammatory (5 cases)

Three patients achieved sperm counts exceeding 10 million per ml and their wives became pregnant (Figs. 1, 2 and 3). Case 1 had had venereal disease; at exploration a right epididymal block with 2 blocks in the right vas were found together with a left epididymal block. Histological examination of the excised segment of vas showed a post-inflammatory stricture. Case 2 initially denied venereal disease, but on confidential questioning, once the successful result was established, he admitted previous infection. This man was classified separately in the previous report since his folic acid levels were low and there was doubt about the adequacy of his diet. Case 3 had had infection which left him with an atrophic left testis and a blocked right epididymis. It should be noted that all 3 patients initially had negative

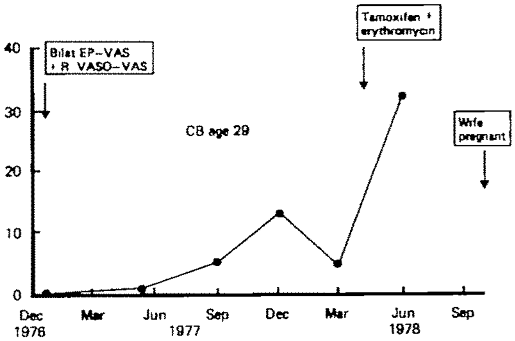

Fig. 1.

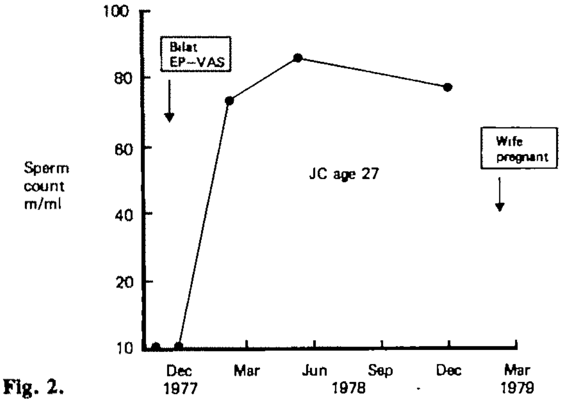

Fig. 2.

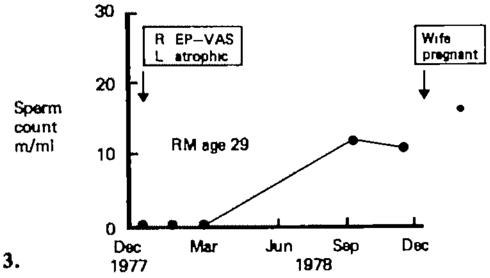

Fig. 3.

Figs. 1, 2 and 3 Serial sperm counts (millions per ml) in Cases 1, 2 and 3 before and after epididymovasostomies (see text for details). Note that at least one negative result was observed after operation in all cases before improvement occurred.

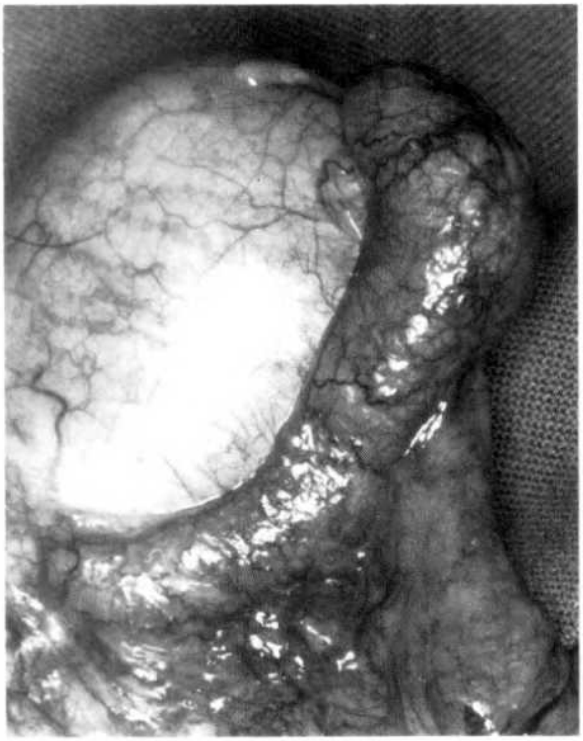

Fig. 4 Epididymis with dilated tubules throughout its length, right down to the tail: appearance typical of post-inflammatory block (Type 3).

post-operative sperm counts which improved only slowly over the ensuing year in 2 of the 3 cases.

All 5 cases in this category had epididymes which were distended evenly down to their tails (Fig. 4), from which pearly white fluid ran freely on incision. Three of 5 had coexisting vasal blocks defined by vasography (Fig. 5).

Group 4—Coexisting Sinusitis, Bronchitis or Bronchiectasis (Young's Syndrome)

A few poorly motile sperms appeared in the ejaculate in 6 cases; the rest remained negative (Table 1). No wives became pregnant. The associated respiratory diseases and results of investigation in this group were described in detail in the previous report.

Table 1 Results in Patients with Young's Syndrome

	Number	*Sperm count*	
		0	*≤1 m/ml*
Sinusitis	5	2	3
Bronchitis	7	5	2
Bronchiectasis	3	2	1

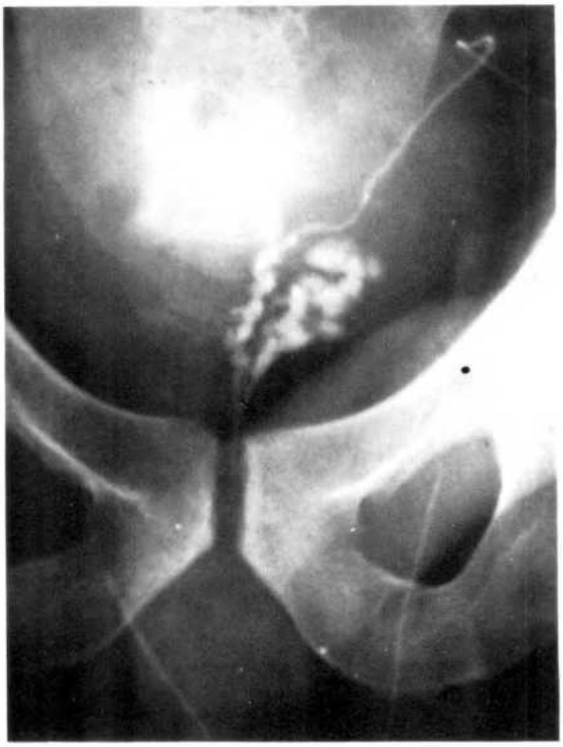

Fig. 5 Vasogram in a post-inflammatory (Type 3) case: there is coexisting obstruction of the right vas.

In all 15 cases the distension of the tubules was confined to the proximal 1.0 to 1.5 cm of the heads of the epididymes, and were empty in the lower parts of their bodies and tails (Fig. 6). The dilated tubules were filled with thick creamy-yellow fluid. Degenerated sperms, debris and cholesterol clefts were seen microscopically in tubules that were lined by cilia with the normal $9+2$ arrangement of microtubules and dynein arms were present. Vasograms were normal in all cases.

Surgical Controls—Reversal of Vasectomy (16 cases)

Ten (62%) successful results were obtained, with pregnancies occurring in the partners up to 2 years after surgery (Table 2).

Table 2 Time to Production of Pregnancy after Vasectomy Reversal

Time (months) to production of pregnancy			
0-3	*4-6*	*6-12*	*13+*
2	3	4	1

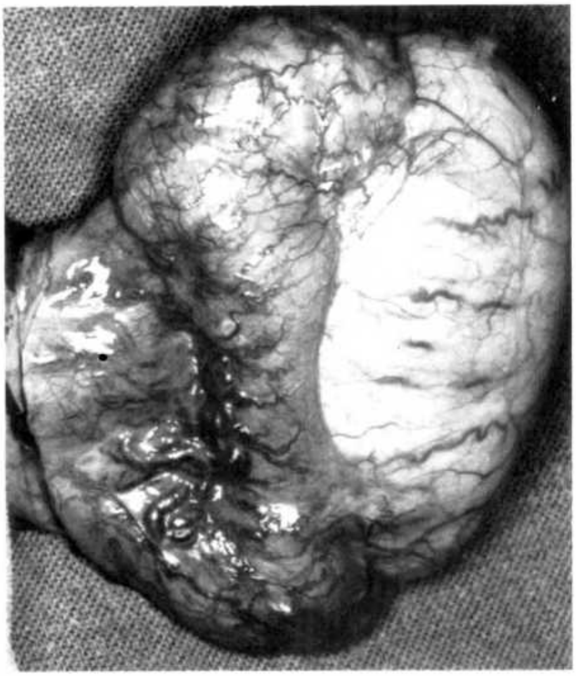

Fig. 6 Epididymis with dilated tubules confined to the head, but body and tail empty: appearance typical of Young's syndrome (Type 4).

Discussion

Correlation of the findings at operation with previous history, coexisting medical findings and subsequent course allowed the construction of a broad classification of obstructive azoospermia (Table 3). The cases are grouped in the order in which the categories will be encountered at operation if the operation is done in logical sequence. If the epididymes are empty (Type 1) only a testicular biopsy is necessary: it is important not to create obstruction in patients who may have maturation arrest that could respond to gonadotrophins (Pryor *et al.*, 1978). If the vasa are absent or malformed (Type 2) this will be discovered as the vasogram is attempted. If the epididymes are full all the way down to their tails the operation may succeed; because the aetiology was almost certainly inflammatory, however, the vasa must be checked, since there is a high chance of coexisting vasal blocks which need to be corrected. If only the heads of the epididymes are distended the prognosis is poor and the surgeon should ask, as Young did in 1970, why so many of these patients have coexisting naso-respiratory disease.

It appears that the level of the block in the epididymis, and the success or failure of epididymovasostomy, depend on the nature of the underlying disease process as suggested by Hanley and Hodges (1968), rather than simply upon the distance travelled through the epididymis as proposed by Schoysman (1978), although it is clear that these 2 factors are related. It is important to note that a history of venereal disease may not be forthcoming in some men with post-inflammatory blocks and our case 2 illustrates that this information may be concealed. Since this study was completed we have seen men with bronchitis who had had venereal disease and acquired post-inflammatory blocks. It is therefore important to explore azoospermic men with normal testes, normal FSH levels and palpable vasa and it is wrong to suppose that the history alone serves to exclude the possibility of operative correction of an acquired block. A scrotal exploration through a short midline incision takes little time, morbidity is minimal and the findings are generally clear-cut. A permanent record of the findings can be made by testicular biopsy, photograph of the epididymis and vasogram if appropriate. Obviously it is most convenient to go ahead with the epididymovasovasostomy in appropriate cases at the same operation.

The surgical technique of side-to-side anastomosis with continuous 6/0 Prolene and no splint has given good results, with a success rate of about 60% (3 out of 5) in the post-inflammatory group. This is comparable with the success rate of 65% reported by Hanley and Hodges (1968), and equivalent to the success rate of 62% in the 16 patients having bilateral vasovasostomies for vasectomy reversal by the same technique. The similarity of these results means that inadequate

Table 3 A Classification of Obstructive Azoospermia Based Upon Aetiology, Findings and Results

Type	*Epididymis*	*Vasa*	*Surgery successful*
1. Empty epididymes	Empty	Normal	0/3
2. Malformed vasa	Full	Absent or malformed	0/7*
3. Post-inflammatory	Full down to tail	May be blocked	3/5
4. Young's syndrome	Only the head filled	Normal	0/15*

*A few poorly motile sperms appeared in some cases.

surgical technique is unlikely to be the cause of failure of so many of the other epididymovasostomies, and provides strong evidence for a fundamentally different cause of failure of sperm transport in cases where the sperms are confined to the head of the epididymis.

The association between obstructive azoospermia and sinusitis, bronchitis or bronchiectasis was first noted by Young (1970); it occurred in 54% of his cases and in 50% in this series. In these cases the spermatozoa are confined to the heads of the epididymes, which are in fact the ductuli efferentes, lined by true cilia, and microscopically distinct from the epididymal ducts lined by stereocilia (more correctly called microvilli). Normally, the sperms pass quickly through the ductuli efferentes and much more slowly through the epididymal ducts where they mature. Microscopically, the ductuli efferentes in Young's syndrome are plugged with spermatozoa. debris and cholesterol clefts suggesting inspissated lipid material. McConnell (1981) has described these changes well and pointed out that they are not seen in patients with absent vasa, suggesting that obstruction is not the only cause of the problem. The association with diseases of the naso-respiratory passages suggests that the problem must lie with the cilia with which both passages are lined, but the cilia probably contribute little to sperm transport in the efferent ducts (Winet, 1980) and sperms are transported normally in the immotile-cilia syndrome (Eliasson *et al.*, 1977). These 2 syndromes are quite different, since in Young's syndrome the cilia are ultrastructurally normal, and preliminary studies of beat frequency of nasal cilia have been normal by the technique of Rutland and Cole (1980) (Rutland, personal communication). Nevertheless, these patients have significantly impaired lung muco-ciliary clearance (Pavia *et al.*, 1981). The cause remains obscure and is the subject of continuing research.

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The Aetiology and Investigation of Haemospermia

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Summary—The cause of haemospermia was determined in 70 (86%) of 81 patients. Inflammatory lesions accounted for the bleeding in most men under 30 years of age. Neoplasia (6), trauma (3) and amyloidosis (2) of the seminal vesicle were diagnosed in the other patients.

Persistent haemospermia should always be investigated since clinically unsuspected tumours may be the source of bleeding in the older age groups. Analysis of the semen, prostatic fluid and urine should be performed initially. Cystourethroscopy should then be carried out if the initial investigations are negative and, if this too is negative, vasography is indicated.

Haemospermia is often regarded as a symptom of little significance and one that merits only a routine clinical examination and urine analysis particularly if there are no other associated urological problems.

Although recognised for centuries and mentioned in the writings of both Galen and Paré, haemospermia has received little subsequent attention in the literature. In a comprehensive review Parker (1942) attempted a classification based on many isolated cases and listed causes including bacterial infections of the genitourinary tract, trauma including orchiectomy, urethral stricture, hypertension, haemorrhoids, scurvy, angiomas of the urethra and seminal vesicles, tuberculosis and bilharzia and sexual excess including "unbridled licence short of physical indulgence".

There are, however, only a few series reported (Yada, 1963; Ross, 1969; Leary and Aguil, 1974; Tolley and Castro, 1975; Yu *et al.*, 1977) and these emphasise the benign nature of the condition and that many patients have essential or idiopathic haemospermia in which no cause can be found.

We have studied a series of patients with haemospermia in an attempt to identify the underlying cause and to outline a plan for investigation and management.

Patients and Methods

Eighty-one patients with haemospermia have been seen at St Peter's and King's College Hospitals between 1976 and 1980. The mean age was 40 years (range 15-73). The length of history, type and frequency of haemospermia and other urological symptoms were recorded. Clinical examination with particular note of testicular and epididymal swelling and digital rectal examination were performed in all cases.

Further investigations included urine analysis, usually after prostatic massage, for routine culture and also for acid fast bacilli in some patients, seminal analysis, intravenous urography, urethrocystoscopy with visualisation of the ejaculatory ducts during vesicular massage, prostatic biopsy as indicated and vasography in selected patients.

A diagnosis of prostatitis or seminal vesiculitis was made on the basis of history, clinical examination with findings of a tender boggy prostate, prostatic fluid examination and urine analysis after prostatic massage, seminal analysis, urethroscopy and vasographic findings.

Results

In 32 patients (39%) haemospermia was the only symptom. The remaining patients had various symptoms of dysuria, ejaculatory pain, testicular, perineal or suprapubic discomfort or prostatism, as might be expected in men over the age of 50. Haematuria was present in 15 patients and was associated with inflammation in 11, a urethral stricture in one and with a papillary tumour of the bladder in another. In 2 patients the bleeding came from prostatic veins.

The results of the various investigations are shown in Table 1. Urine analysis was performed in most patients, but not always following prostatic

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Table 1 Investigation of Haemospermia

Investigation	*Number*	*Number positive (%)*
Seminal analysis	41	22 (54%)
Cystourethroscopy	52	26 (50%)
Vasography	22	16 (73%)
(Prostatic biopsy)	7	—
MSU	76	22 (29%)
IVU	58	4 (6%)

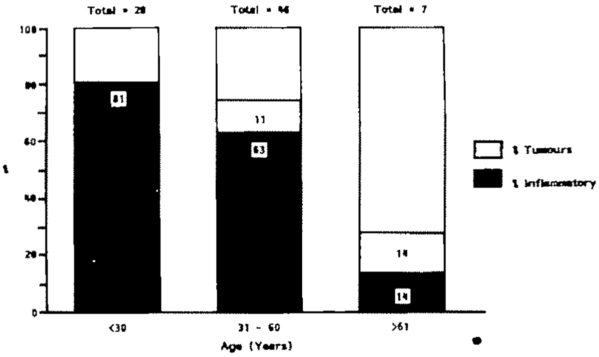

Fig. Age related causes for haemospermia. The incidence of inflammatory causes is highest in patients under 30 years of age. Neoplastic causes occurred in the older age group.

massage, and pus or red cells or a significant culture were found in only 22 patients (27%). Intravenous urography was performed in 58 patients but was of little value even when there was coexistent haematuria. Seminal analysis was performed in 41 patients and abnormalities found in over 50%. Prostatic biopsy showed features of benign hyperplasia in 7 patients.

A cause for the haemospermia was found in 70 patients (86%) (Table 2). In 80% infection was the cause, particularly in patients under 30 years of age (Fig.). Forty-one (54%) had prostatitis or seminal vesiculitis, 12 (15%) had epididymo-orchitis and one had extensive urethral condylomata. No patient had tuberculosis or bilharzia. Seminal analysis of these patients showed pyuria in 50% and a positive culture in 30%.

At urethroscopy the prostatic urethra was found to be hyperaemic and oedematous in 60% of these patients, with a patchy polypoid appearance in some cases, which was confirmed as inflammatory by biopsy in 4. Prostatic calculi were noted under the mucosa of the prostatic urethra and in the mouth of the ejaculatory ducts in some patients. The vasogram was abnormal in 12 of the 15 patients in whom it was performed. The haemospermia usually resolved in this group of patients following treatment of infection with rotating courses of antibiotics. The patient with urethral condylomata responded dramatically to treatment with 5% 5-fluorouracil cream to the urethra (Dretler and Klein, 1975).

Six patients (8%) were found unexpectedly to have neoplastic disease—3 had prostatic carcinoma, 2 had superficial papillary transitional cell carcinomas of the bladder and one had extensive low grade papillary tumours of the urethra extending to the bladder neck.

Table 2 Diagnosis in 81 Patients with Haemospermia

Inflammatory	54
Trauma	3
Neoplastic	6
Miscellaneous	7
Unknown	11

In 3 patients the haemospermia was associated with trauma—in one following haemorrhoidal injection and one each with testicular trauma and traumatic Peyronie's disease. Seven patients had miscellaneous causes including urethral stricture (1) and benign prostatic hypertrophy or prominent veins at the bladder neck (4). Two patients had amyloidosis of the seminal vesicles discovered histologically following excision of the vesicles because of gross abnormalities on vasograms performed for persistent haemospermia. No cause was found in 11 patients (14%) who were classed as having essential or idiopathic haemospermia and the bleeding in these patients was not considered to be due to hypertension.

Discussion

In contrast to other series, we have been able to identify a cause of bleeding in over 80% of patients and in only a small number was it necessary to classify them as having essential haemospermia. The majority of patients, particularly those under the age of 30, had an inflammatory cause. There has been a significant proportion of patients with tuberculosis in reported series (Yada, 1963; Ross, 1969; Yu *et al.*, 1977) but we found no evidence of this in our patients.

Six patients over the age of 40 were found to have neoplastic disease which was not expected on clinical grounds and this suggests that haemospermia should be thoroughly investigated, particularly if persistent in the older age group. Dermarquay (Parker, 1942) first mentioned that haemospermia may follow orchiectomy from bleeding into the stump of the vas and presumably direct testicular trauma causes it in a similar manner. Occasionally a testicular tumour may also present in this way (Hope-Stone *et al.*, 1963). Hugues (Parker, 1942) suggested that sudden cessation of bleeding from piles and opening of venous connections between the prostatic plexus and haemorrhoidal veins in patients with portal hypertension could cause haemospermia. In our patient it is likely that direct puncture of the vesicles occurred at the time of haemorrhoidal injection.

Among patients with significant disease of the seminal vesicles haemospermia is a rare symptom (Ewell, 1963; Heller and Whitesel, 1963; Smith *et al.*, 1967; Tripathi and Dick, 1969) and it was therefore unusual to find 2 of our patients with amyloid disease. Neither had evidence of systemic disease and in one there was a history of a prostatic abscess in the past which may have been a contributory factor.

Despite investigations there remains a group of patients with idiopathic or essential haemospermia in whom no cause can be found (Ross, 1969). It would appear that in most cases the bleeding is from the vesicles rather than the prostate (Huggins and McDonald, 1945) and it has been suggested that sudden emptying of a distended vesicle during ejaculation causes a haemorrhage analogous to the bleeding that occurs after decompression of a chronically distended bladder (Parker, 1942).

Both Yada (1963) and Magid and Hejtmancik (1957) demonstrated radiologically a direct communication between the vesicles and the iliac veins in patients with haemospermia, possibly due to vascular venous anomalies with erosion of the seminal vesicles by ulceration. Our studies have thrown no further light on the aetiology of idiopathic haemospermia and no venous connections were demonstrated on the vasograms in our patients.

The benign nature of haemospermia is well recognised, particularly if there are no other associated symptoms. Even when patients with haemospermia subsequently developed urological disease it was often thought that the disease was unrelated to the haemospermia (Leary and Aguil, 1974). Our studies indicate that a cause can be found in most patients and that in those under 30 years of age this is almost invariably inflammatory.

The initial investigations of haemospermia should consist of analysis of the urine, semen and prostatic fluid. The persistence of unexplained haemospermia merits cystourethroscopy and, if no cause for the bleeding has been found, vasography should be performed under the same anaesthetic. Intravenous urography rarely provides any useful information.

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The Urodynamic Characteristics of Multiple Sclerosis

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Summary—Urodynamic assessment was performed in 52 patients with urinary symptoms positively diagnosed as suffering from multiple sclerosis. Fifty-one patients had unequivocal bladder instability on filling cystometry the exception had inappropriate relaxation of the urethral sphincter at a small bladder capacity and low bladder pressure. Results of sphincter electromyography and synchronous cineradiography of voiding in a number of our patients led to the conclusion that many of these patients also suffer detrusor sphincter dyssynergia. There was no correlation between any measurable urodynamic parameter and the severity of the physical disability.

Multiple sclerosis (MS) is the commonest organic neurological disease affecting young adults in the western hemisphere and urinary symptoms are the commonest and most socially disabling feature. Miller *et al.* in 1965 investigated the prevalence of urinary symptoms in a representative population of 297 MS patients on Tyneside: 78% of these had symptoms at some stage in their illness and these had persisted in 52%. The severity of urinary symptoms was found to correlate only with the degree of disability and not to the duration of either these symptoms or the disease. The increasing use of bladder pressure measurements in diagnosis has resulted in a number of reports on the urodynamics of MS which show between 56 and 74% of patients to have unstable and 5 and 40% of patients to have atonic bladders (Table 1). None of these reports gave details of the severity of the neurological condition in their patients. Jameson (1977), however, commented in a review article that in his experience atonic bladders are a rare finding in MS even in advanced cases.

In a population of ambulant MS patients referred for urological investigation we found no patient with an atonic bladder. It seemed reasonable to assume that the development of atonia could be a feature of end-stage disease and we therefore investigated a further group of patients with severe disability attending a young chronic disabled unit.

Patients and Methods

Fifty-two patients with urinary symptoms were investigated, all of whom had been diagnosed as suffering from multiple sclerosis on the criteria of Schumacher (1965). Patients underwent a full neurological examination and their degree of physical disability was graded according to the classification of Kurtzke (1965), a system in which increasing total disability is scored on a scale from 0 (no disability) to 10 (dead of MS). The urodynamic investigation followed a standard pattern. If possible a free flow study with the patient sitting on a commode or standing was performed on arrival. Patients were then catheterised and residual urine measured. With the bladder empty, supine urethral pressure profiles at rest and during voluntary squeeze were obtained via a Porges 8 FG pressure profile catheter perfused at 2 ml/min, the catheter being mechanically withdrawn at 1 cm/s. Patients were then re-catheterised with a straight 8 or 10 FG plastic catheter (for filling) and a 5 FG neonatal feeding tube (for bladder pressures). Simultaneous rectal pressures were measured via a 6 FG water filled plastic tube, the end protected with a finger cot. Pressures were measured via AV300/1 physiological pressure transducers and recorded on a Mingograf 800 ink jet recorder. Supine and where possible erect cystometry was then performed using saline at room temperature infused at 100 ml/min, occasionally repeated at 20 ml/min. Electromyography of the external urethral sphincter, recorded with a coaxial needle introduced percutaneously, was performed satisfactorily in 12

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Table 1 Urodynamics of Multiple Sclerosis

Authors (USA)	*Year*	*Number of patients*	*Methods*	*Per cent unstable bladders*	*Per cent atonic bladders*
Bradley *et al.*	1973				
Anderson and Bradley	1976	302	Gas cystometry	62	34
Bradley	1978		Anal plug EMG		
Summers	1978	50	?	64	12
Piazza and Diokno	1979	31	Water cystometry sphincter EMG	74	13
Blaivas *et al.*	1979	45	Water cystometry	56	40
Schoenberg *et al.*	1979	39	Gas cystometry	74	5

patients. Cineradiography of a void with simultaneous pressure measurements augmented the study in a further 6 patients. Definitions conform to the ICS standards.

Results

Of the 52 patients 23 were male, 29 female. The age and sex ratios are shown in Figure 1. Their distribution according to physical disability is presented in Figure 2; there was a preponderance of patients who were significantly disabled (grades 6 to 9). The length of history ranged from 2 to 36 years with an average of 10 years, and urinary symptoms from 3 months to 15 years with an average of 5 years. The urinary symptoms were the presenting complaint in 4 patients, one acute retention, 2 with urge incontinence and one thought to have outflow obstruction but with symptoms of frequency, urgency and nocturia.

Table 2 shows the incidence of symptoms at the time of the investigations. Urgency and frequency were the most common complaints (61 and 59% of all patients): 25% experienced voiding difficulties (hesitancy and/or intermittent stream) and 11 patients (21%) had suffered episodes of retention, most requiring catheterisation for relief. Fifteen patients (28% of the total) had indwelling catheters at the time of the investigation; 4 (8%) were catheterised for acute retention and 11 (21%) for incontinence. Three-quarters of these latter patients experienced significant problems directly related to the presence of the catheter; 5 had uncontrolled bladder spasms with leakage around the catheter; 3 suffered recurrent blockage and infections.

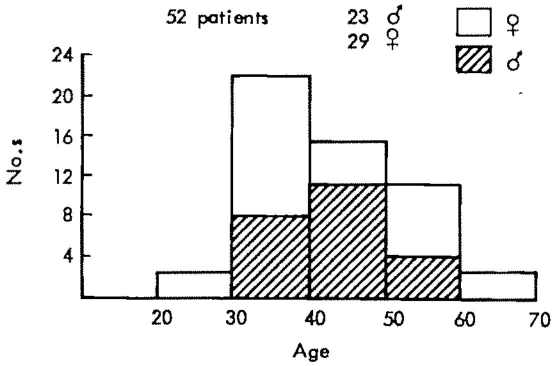

Fig. 1 Age and sex distribution in 52 MS patients.

These figures accord with other published series. There was no difference in the incidence of the various symptoms between any of the physical disability subgroups, except that all patients catheterised for incontinence occupied grades 6 to 9.

Urodynamically, all but one patient had bladder instability on filling. The exception, who had been catheterised for the previous 4 years but who continued to leak freely, showed a slow pressure rise on filling.

At 12 cm H_2O subtracted pressure, which corresponded to 50 ml infused, there was free leakage around the catheter and the bladder emptied without further pressure rise (Fig. 3). This was consistently reproducible and was not considered to be atonia but inappropriate relaxation of the urethral sphincter at low bladder pressure.

Free flow studies, residual urine estimations,

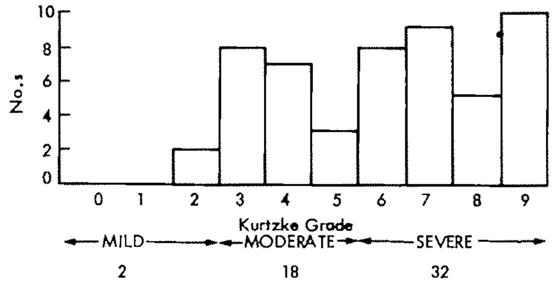

Fig. 2 Distribution of physical disabilities in patients with MS.

Table 2 Symptoms at the Time of Investigation

Symptom	*Number total 52*	*Percentage*	
Frequency	30	59	
Urgency	31	61	
Urge incontinence	24	47	
Nocturia	27	53	
Enuresis	13	25	
Voiding difficulties	13	25	
Retention—episodic	11	21	2 previous BNI 1 previous TURBN
—acute	4	8	
Indwelling catheter for incontinence	11	21	

maximum urethral closure pressures and augmentation with voluntary squeeze, maximum bladder capacity and maximum and voiding detrusor pressures were also analysed against disability grades.

There were wide variations within each disability subgroup and apart from a tendency for the bladder capacity to fall in the severest grades of disability, there was no correlation between any finding and the degree of disability.

Satisfactory sphincter EMG recordings were obtained in 12 patients, 5 in the moderate and 7 in the severe disability groups. Analysis of symptoms and findings showed these patients to be representative of the series as a whole. Each EMG showed unequivocal detrusor sphincter dyssynergia. Cineradiography with synchronous pressure measurements of a void supported a diagnosis of detrusor sphincter dyssynergia in a further 4 patients, while 2 others were judged to be normal.

Discussion

The most surprising finding was the complete absence of atonia in the 52 patients. From other reported series between 2 and 20 people should have been expected to have flaccid bladders, yet the range of symptoms in this series was comparable with other reports and we have studied patients in all categories of physical disability, as defined by Kurtzke (1965), in which bladder symptoms occur. Moreover, although there were marked variations in individual urodynamic measurements between patients, all but one conformed to a pattern, namely unequivocal bladder instability on filling. Detrusor sphincter dyssynergia was confirmed by EMG or cineradiography in 16 out of 18 patients who were able to void under the circumstances of the test.

The bladder lesion in multiple sclerosis on theoretical grounds should be an unstable detrusor with sphincter dyssynergia. Oppenheimer (1978), in the largest published series on the distribution of MS plaques in the spinal cord, demonstrated lesions in the cervical cord in all of his cases. The frequency of lesions in the cord below this was significantly less: only 41% had plaques in the lumbar cord. In the cervical cord these lesions commonly showed a lateral white matter fan-like distribution which tended to include the 3 reticulospinal tracts concerned with bladder control. He did not report on the conus medullaris but we have subsequently reviewed his material and could find plaques in this region in only 3 of his 17 cases (18%).

The demyelinating lesions themselves do not affect axon cell bodies directly and, experimentally, it has been shown that conduction is not halted but slowed through areas of demyelination giving rise to temporo-spatial disruption of the normal pattern of descending impulses and hence a physiological upper motor neurone lesion. Lower motor neurone lesions in the limbs, ascribed to root entry plaques, are exceptionally rare even in the upper limb served by the area of cord where plaques invariably occur. It therefore seems un-

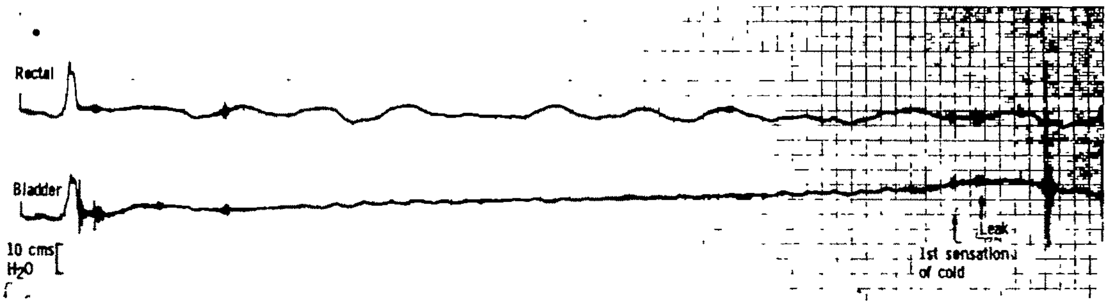

Fig. 3 Filling CMG trace of patient WD showing slow pressure rise to 12 cm H_2O when free leakage occurred.

likely that the neurological lesion in MS could produce the sort of bladder picture seen, for example, in traumatic lesions of the sacral cord (Denny-Brown and Robertson, 1933).

One possible explanation for the apparent discrepancy between published series lies in the nature of the underlying disease and the frequent difficulty with which the diagnosis of MS is made, namely by exclusion and observation of progression over time of a dispersed pattern of lesions for which there is no other explanation. The definitive diagnosis can only be made at post mortem. On clinical grounds various categories of diagnostic certainty are well defined, those of Schumacher (1965) being the most widely used.

This difficulty in diagnosis is illustrated by the Winnipeg experience. In 1951 an attempt was made to identify all cases of MS in the Winnipeg area. Ten years later 149 of these cases in which MS was the principal diagnosis were re-examined (Stazio *et al.*, 1964). Of 112 patients positively diagnosed as suffering from MS only 85 were accepted 10 years later (76%). In addition, none of the patients in whom MS was the most likely diagnosis in 1951 were accepted as suffering from the disease on re-examination.

None of the other series on urodynamic findings in patients with MS gives any information on the diagnostic criteria used to identify their cases, and it is a reasonable assumption that their MS patients were diluted by a significant proportion of patients who did not in fact have the disease.

The way in which the patients were selected by strictly defined diagnostic criteria for this study would have largely removed this potential source of error.

On the basis of the present findings it is not possible to confirm the suggestion that atonia is a feature even of end-stage disease; indeed, it seems likely that on both theoretical grounds and our observations the atonic bladder is not a primary neurological feature of multiple sclerosis. It is conceivable that urodynamic findings may influence neurological diagnosis in patients suspected of having MS.

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Prizes and Awards

British Association of Urological Surgeons: Annual Meeting London. 8-10 July 1981

President: W. Keith Yeates

St Peter's Medal

At the Annual Dinner the President presented St Peter's Medal to Dr R. C. B. Pugh, of the Institute of Urology, after a citation given by Mr D. M. Wallace.

Berk Pharmaceuticals Lecture

This Guest Lecture, entitled "The functional anatomy of the human urinary tract", was given by Professor John A. Gosling, Professor of Anatomy, University of Manchester.

C. R. Bard Award

This prize is given to the author who, in the opinion of a panel nominated by Council, has presented the best paper at the Annual Meeting: it consists of a cheque for £350 and a Silver Medal. The prize was awarded to Surgeon Commander A. C. Buck for the paper entitled "The influence of renal prostaglandins on glomerular filtration rate (GFR) and calcium excretion in urolithiasis" by A. C. Buck, W. F. Sampson, C. J. Lote and N. J. Blacklock.

Eschmann Prize

This prize of £250 for the best Scientific Exhibit was awarded to Mr C. P. Chilton for his demonstration of "The distal male urethral sphincter and its relation to the pelvic floor musculature".

BAUS Travelling Fellowship

The British Association of Urological Surgeons offers a Travelling Fellowship of £500 for the best article in each volume of the *British Journal of Urology,* provided that it is of outstanding merit. Candidates for the prize must be Fellows of one of the Royal Colleges of Surgeons in the British Isles, Canada, Australasia, or South Africa; they must be undergoing urological training or have obtained a consultant post not more than 10 years before the date of submission of the paper. In the case of multiple authorships the authors would have to decide which of them should receive the prize. The successful prizewinner must submit a programme of visits to Urological Centres outside Britain for consideration by the Council.

The 1981 prize for the best article in Volume 52, 1980, was awarded to Mr T. B. Hargreave for the article entitled "The significance of serum sperm-agglutinating antibodies in men with infertile marriages" by T. B. Hargreave, M. Haxton, J. Whitelaw, R. Elton and G. D. Chisholm, *British Journal of Urology* (1980), **52**, 566-570.

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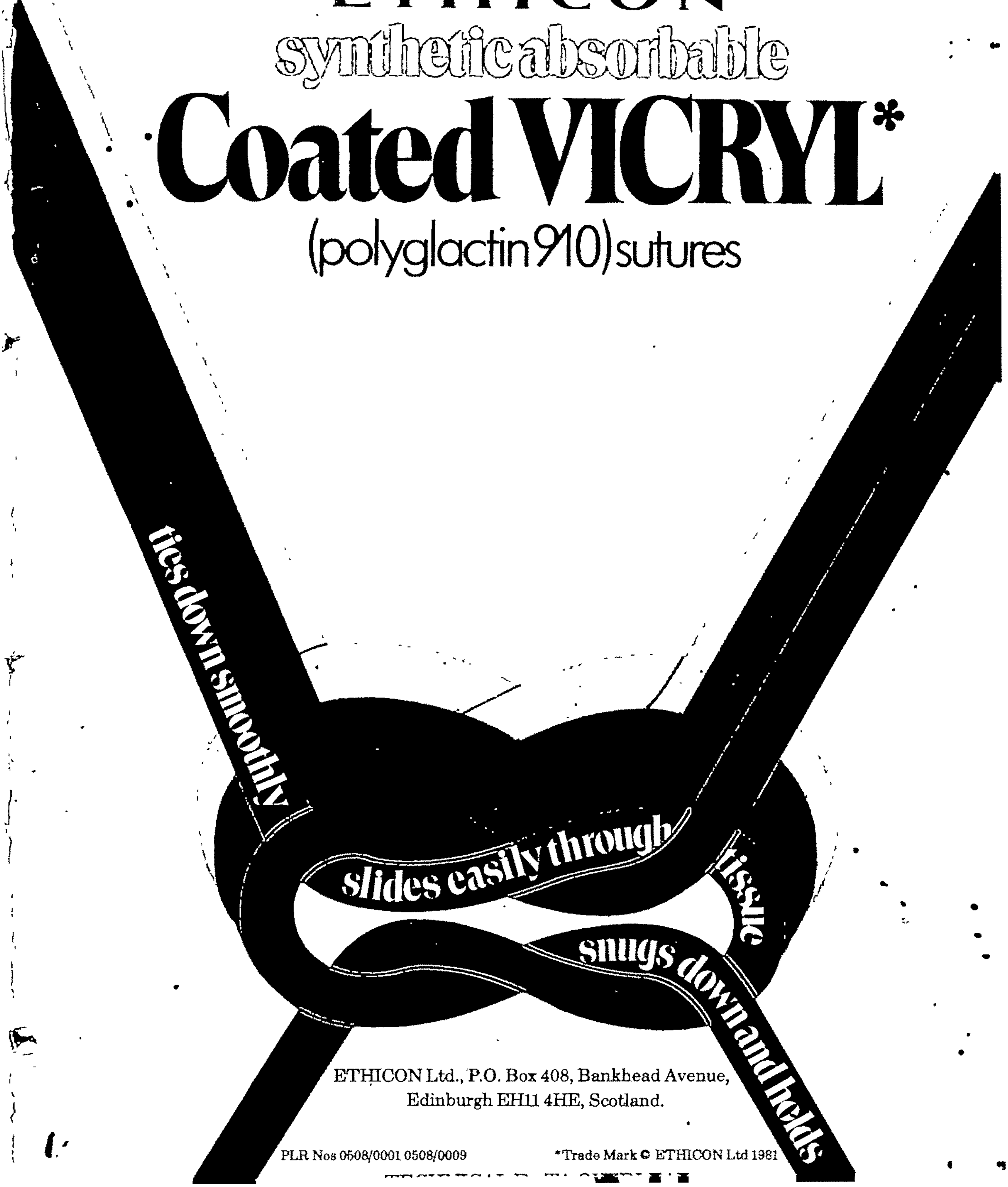

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TECHNICAL DATA

STERILISED ABSORBABLE SYNTHETIC SUTURE COATED POLYGLACTIN 910 VICRYL*

Presentation The basic VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)m(C_3H_4O_2)n$

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided suture material with a mixture composed of a copolymer of glycolide and lactide and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Suture may also be manufactured in the undyed form

These sutures are relatively inert, nonantigenic, nonpyrogenic and elicit only a mild tissue reaction during absorption

Action Two important characteristics describe the in vivo behaviour of absorbable sutures The first of these is tensile strength retention and the second absorption rate or loss of mass.

Subcutaneous tissue implantation studies of both VICRYL and Coated VICRYL Suture in rats show at two weeks post-implantation approximately 55% of its original tensile strength remains, while at three weeks approximately 20% of its original strength is retained

Intramuscular implantation studies in rats show that the absorption of these sutures is minimal until about the 40th post-implantation day. Absorption is essentially complete between the 60th and 90th days.

Uses VICRYL and Coated VICRYL synthetic absorbable sutures are intended for use where an absorbable suture or ligature is indicated

Dosage and Administration
By implantation.

Contraindications, Warnings, etc.
These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 10 days and should be removed as indicated.

The safety and effectiveness of VICRYL (Polyglactin 910) and Coated VICRYL Sutures in neural tissue and in cardio-vascular tissue have not been established

Pharmaceutical Precautions
Do not re-sterilise.

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582 Prophylactic Oral Methotrexate Therapy for Multiple Superficial Bladder Carcinoma
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